69. ***OAR:*** When does EPA anticipate completing this review, and what does it hope to accomplish through this review?

70. ***OAR:*** What steps is EPA taking to ensure these actions do not negatively impact cellulosic biofuel volumes in the 2019 RVO rulemaking?

Senator Markey:

WEBSITE

71. ***OPA:*** In all, more than 5,000 pages of scientific, policy, and educational material on climate change have been moved off the main website for the Environmental Protection Agency (EPA). This information has been largely relegated to a maze of archives and portals that is virtually inaccessible to the public. The EPA's mission states that the agency should ensure "all parts of society – communities, individuals, businesses, and state, local and tribal governments – have access to accurate information sufficient to effectively participate in managing human health and environmental risks."[25] Additionally, the Paperwork Reduction Act directs agencies to "provide adequate notice when initiating, substantially modifying, or terminating significant information dissemination products."[26] However, there was no notice of the changes made to the EPA website, leaving the public with no opportunity to weigh in on the Administrator's decision to move, hide, and archive information on the Clean Power Plan or on climate change.
    a. How does the decision to remove hundreds of webpages and post the notice on the same day comply with the EPA's mission?
    b. How does the decision to remove hundreds of webpages and post the notice on the same day comply with the Paperwork Reduction Act?
    c. Were you personally involved in directing the removal of any information from the EPA website? If so, please provide any correspondence or documentation relating to your personal involvement in the overhaul and censorship of the EPA website.

72. ***OPA:*** The error page on the EPA website that the public reaches when trying to access former resources on climate change reads, "This page is being updated [...] We are currently updating our website to reflect EPA's priorities under the leadership of President Trump and Administrator Pruitt."
    a. Please provide a timeline for when this update will be complete, as well as a detailed list of all the pages that have been permanently removed from www.epa.gov and the changes made on those that remain in an altered form.
    b. Please explain how the priorities of President Trump and Administrator Pruitt necessitate the removal of pages like "What Climate Change Means for Massachusetts" from www.epa.gov.

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[25] "Our Mission and What We Do." United States Environmental Protection Agency. Accessed February 1, 2018. https://www.epa.gov/aboutepa/our-mission-and-what-we-do

[26] 44 USC § 3506(d)(3)

c. Please provide an accounting of the costs and employee hours associated with developing the resources that were removed, as well as with the process of moving and updating the website to "reflect EPA's priorities."

ENFORCEMENT

73. ***OECA:*** Oklahoma recently suffered what may be the deadliest accident in the history of the shale industry, when five workers were killed by an explosion at a fracking site. The company that owns this site (Patterson-UTI) has reportedly experienced several other deadly safety incidents from 2010-2013. Oklahoma's regulators use an enforcement system that shuns fines in favor of working with violators, a strategy which you appear to have emulated during your tenure. For example, Devon Energy had admitted to illegally emitting hazardous chemicals, and was in discussions to pay a settlement of more than $100,000 and install mitigation technology. After your swearing it, Devon Energy informed the EPA that it was "re-evaluating its settlement posture" and now offered a settlement of around $25,000 with no commitment to install additional technology.[27]

According to a New York Times analysis, compared to the first nine months of the Obama administration, you have: filed roughly 1,000 fewer new enforcement cases; sought 60 percent less in civil penalties; requested almost 90 percent fewer injunctive relief fixes, which prompt companies to cut pollution; and made it harder for EPA offices to request pollution tests.[28]

a. Please provide a list of companies and plants that received notices of violations from 2008-2017 under the Clean Water Act, the Clean Air Act, or the Resource Conservation and Recovery Act, but that have not yet had any EPA penalties levied upon them.
b. Please provide a detailed list of cases where, under your leadership, the EPA withdrew or accepted lower civil monetary penalties than were recommended under the previous administration from 2008-2017 and the rationale for these decisions.

74. ***OECA:*** The EPA recently released data that detailed the fines, penalties, and other commitments that the agency collected during fiscal year 2017.[29] According to the EPA's report, the number of new cases, defendants charged, and federal inspections and evaluations began by the agency in FY2017 were all at the lowest level in at least a decade. Despite this, the EPA still touted an increase in the total amount of criminal fines, including restitution and mitigation activities.

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[27] Brook-Davison, Carrick. "RE: Revised Devon settlement proposal for the Beaver Creek Gas Plant." Guida, Slavich & Flores. February 22, 2017. Accessed February 1, 2018. https://www.documentcloud.org/documents/3727057-Devon-Fights-and-Now-Is-Winning-Battle-Against.html#document/p1/a356485

[28] Lipton, Eric and Danielle Ivory. "Under Trump, E.P.A. Has Slowed Actions Against Polluters, and Put Limits on Enforcement Officers." The New York Times. December 10, 2017. Accessed February 1, 2018. https://www.nytimes.com/2017/12/10/us/politics/pollution-epa-regulations.html

[29] "Enforcement Annual Results for Fiscal Year 2017." Environmental Protection Agency. Accessed February 9, 2018. https://www.epa.gov/enforcement/enforcement-annual-results-fiscal-year-2017

a. Of the cases included in the FY17 reporting, what percentage of fines and restitutions, court ordered environmental projects, Superfund site commitments from liable parties, judicial penalties, injunctive relief, and other penalties were made before January 20, 2017?
b. Of the cases included in the FY17 reporting, what percentage of civil and criminal cases, inspections/evaluations, complaints, and orders were initiated, opened, or filed after January 20, 2017?

75. ***OFCO:*** The EPA FY19 budget request included an 18 percent cut to civil enforcement and a 12 percent cut to criminal enforcement from the FY18 annualized Continuing Resolution (CR).
    a. As the number of new enforcement cases are already falling under your tenure, how does limiting the enforcement budget further facilitate your stated objective to "timely enforce environmental laws to increase compliance rates [...] especially enforcement actions to address environmental violations?[30]
    b. How many full-time EPA employees working on civil, criminal, Superfund, and federal facilities enforcement do you expect to be supported by the FY19 budget request?

CLIMATE IN DRAFT STRATEGIC PLAN

76. ***OPA:*** You have said that "scientists continue to disagree about the degree and extent of global warming and its connection to the actions of mankind."[31] With regard to human-produced carbon dioxide, in an interview with CNBC, you said that, "I would not agree that it's a primary contributor to the global warming that we see."[32] But the statutorily required National Climate Assessment's Climate Science Special Report that was released by the Trump Administration in November concluded that "human activities, especially emissions of greenhouse gases, are the dominant cause of the observed warming since the mid-20th century."[33] Last year was the second-hottest year in recorded history, according to the National Aeronautics and Space Administration, and saw record-breaking costs incurred by extreme weather and climate disasters.
    a. Do you disagree with the conclusion made in the Climate Science Special Report by our country's top scientists at 13 federal agencies, including your own, that human activities are the dominant cause of global warming, with "no convincing alternative explanation"?

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[30] "FY 2019 EPA Budget in Brief." United States Environmental Protection Agency. February 2018. Accessed February 13, 2019. https://www.epa.gov/sites/production/files/2018-02/documents/fy-2019-epa-bib.pdf
[31] Pruitt, Scott and Luther Strange. "The Climate-Change Gang." The National Review. May 17, 2016. Accessed January 31, 2018. http://www.nationalreview.com/article/435470/climate-change-attorneys-general
[32] DiChristopher, Tom. "EPA chief Scott Pruitt says carbon dioxide is not a primary contributor to global warming." CNBC. March 9, 2017. Accessed February 1, 2018. https://www.cnbc.com/2017/03/09/epa-chief-scott-pruitt.html
[33] Wuebbles, D.J., and D.W. Fahey, K.A. Hibbard, D.J. Dokken, B.C. Stewart, and T.K. Maycock (eds.) "Climate Science Special Report." U.S. Global Change and Research Program. November 2017. Accessed January 31, 2018. https://science2017.globalchange.gov/downloads/CSSR2017_FullReport.pdf

77. ***OPA:*** Despite these findings, and the conclusion that "[c]hanges in the characteristics of extreme events are particularly important for human safety,"[34] climate change did not appear in the EPA's Strategic Plan for 2018-2022, as published on February 12, 2018.
    a. Why does climate change not appear in the draft plan?
    b. Do you intend to address climate in other strategic planning documents, commensurate with the findings of the Climate Science Special Report? If not, why not?

PERSONNEL

78. ***OCFO:*** In the FY19 budget request, Science and Technology funding was cut from $708,975,000 in the FY 2018 annualized CR to $448,965,000—a decrease of 37 percent. The Regional Science and Technology funding was zeroed out entirely. This attack on science comes as more than 200 scientists have left the agency over the past year.
    a. How many full-time scientists will be supported at the EPA by the FY19 budget request?
    b. Can you describe how the Regional Science and Technology capabilities will be fully replaced by the "ad hoc" efforts described in the Budget in Brief?

TOXIC CHEMICALS

79. ***OCSPP:*** During the hearing, you committed to updating my office on the status of the formaldehyde health assessment, which I understand has been completed by EPA staff but not yet released.
    a. What date was the draft assessment completed by EPA staff?
    b. What is the exact timeline for public release?
    c. What are the exact steps that EPA must take internally before the report is shared for interagency review?

80. ***ORD:*** The Integrated Risk Information System (IRIS) provides the scientific research needed to effectively implement the Clean Air Act, Clean Water Act, Safe Drinking Water Act, Food Quality Protection Act, and the Toxic Substances Control Act (TSCA), among other laws that protect our nation's public health and environment. However, there have been repeated attacks made on IRIS's objectivity and independence, despite recent changes made to strengthen its scientific approach. There are reportedly around 30 people left working at IRIS, after a period of serious attrition similar to that seen within other EPA offices.
    a. Does the EPA plan on moving the IRIS program from the Office of Research and Development to the Office of Chemical Safety Pollution and Prevention (OCSPP) as reported, thereby placing it within the regulatory arm of the EPA and out of the science and research office?
    b. If yes, please detail how the EPA would ensure that the scientific research remains independent, transparent, and non-politicized.

[34] Ibid.

c. Please provide a list of dates and attendees of meetings you or senior political appointees have taken in which IRIS was discussed, as well as any communication or documents relating to these meetings.

Senator Merkley:

81. ***OPA:*** Under your new policy, you exclude scientists who currently receive EPA grants from serving on EPA scientific advisory committees (link: https://www.epa.gov/sites/production/files/2017-10/documents/final_draft_fac_directive-10.31.2017.pdf).
    a. What is the legal basis for this new directive?
    b. What is your reasoning in exempting tribal, state, and local EPA grant recipients from the directive?
    c. How do you define conflicts of interest within the EPA advisory committees?
    d. Have you consulted with scientific societies, the National Academies, or other independent science organizations about the definition of conflicts of interest?
    e. How will your directive work to ensure that the agency's advisory committees are able to make objective recommendations based on the best available science?
    f. Can you provide an example of a time when a EPA grant recipient on a federal advisory committee provided "conflicted" advice to the administrator?
    g. Now that your directive has tripled the number of industry scientists on the SAB, how will you ensure that the EPA's science advice remains independent?

82. ***OPA:*** The policy excluding scientists does not affect individuals who have industry ties. For example, Dr. Tony Cox received money from American Chemistry Council, American Petroleum Institute, Engine Manufacturers Association, National Mining Association, and many others, yet you selected him to chair the Clean Air Scientific Advisory Committee (CASAC). Why are industry-funded individuals with apparent conflicts of interest more qualified to serve in these science committees than independent scientists?

83. ***OPA:*** You took an unprecedented action and dismissed Dr. Donna Kenski from EPA CASC before her term expired, alleging that Kenski would not qualify under EPA's problematic new policy. Even so, Dr. Kenski's employer, the Lake Michigan Air Directors Consortium's EPA grant is routed through the state government, a category is exempted in the new policy. At the same time, Dr. Michael Honeycutt is allowed to chair the Scientific Advisory Board, even though he has received over $58 million in grants while leading the Texas Commission on Environmental Quality. Why does the same policy disqualifies Dr. Kenski while allowing Dr. Honeycutt to serve?

84. ***OPA:*** You pledged repeatedly in front of this committee that since you are a lawyer and a prosecutor, you would defer to your career staff for science advice. Yet you replaced Dr. Kenski with Dr. Larry Wolk, whom according to your staff's memo, had "no direct experience in health effects of air pollution, epidemiology, toxicology." On Dr. Tony Cox, your staff raised conflict of interest and appearance of a lack of impartiality issues. Will you commit to follow the recommendations of EPA's career staff so no one appointed to the EPA's advisory committees are either unqualified or have conflicts of

interests so that the committees can provide you with the best and sound science that you and the agency so desperately need?

85. ***SAB:*** In your hearing in front of the House Energy & Commerce Committee, you said that EPA has issued $77 million in grant money to twenty members of the EPA scientific advisory committees. Please provide detailed information behind this statement, including the names of the 20 members, their affiliations, their EPA-funded projects and grant amount.

86. ***OPA/ORD:*** During your nomination hearing, you said that you "have no first-hand knowledge" of the EPA's scientific integrity policy at the time. However, you did commit to "thoroughly reviewing" the policy and following "federal guidance regarding scientific integrity." The policy states that EPA scientists are free to "exercise their right to express their personal views provided they specify they are not speaking on behalf of…" the EPA (Link: https://www.epa.gov/sites/production/files/2014-02/documents/scientific_integrity_policy_2012.pdf). Have you reviewed and implemented this part of the policy? Can you affirm that EPA scientists and managers are free to exercise their right to express their personal views free from political interference, as guaranteed by this policy?

87. ***OPA/ORD:*** The EPA's scientific integrity policy encourages EPA scientists to engage with their peers in the industry, academia, government, and non-governmental organizations as long as it is consistent with their job duties. The policy explicitly states that this can include presenting their work at scientific meetings and actively participating in professional societies, and more. However, 3 EPA scientists that were scheduled to speak at a conference on climate change at Narragansett Estuary Bay were restricted [link:https://www.ucsusa.org/center-science-and-democracy/attacks-on-science/accumulating-evidence-federal-scientists-are-being#.WnDaRq6nFhF] from attending, in direct conflict with the agency's scientific integrity policy.
    a. Did you realize that this decision was in violation of the policy?
    b. Will you commit to ensuring that this type of flagrant violation will not happen again under your watch?
    c. In the spirit of upholding scientific integrity in EPA decision making, will you commit to not politically interfere in science-based policy decisions at the agency, yes or no?

88. ***OAR:*** You decided to postpone steam electric power plant effluent guidelines rule in September. Who are the stakeholders that you met with prior to making this decision? Additionally, please provide the analyses that helped you make this decision.

89. ***OCSPP:*** Please explain why the EPA removed methylene chloride, NMP, and TCE from the Unified Agenda of Regulatory and Deregulatory Actions.

90. ***OCSPP:*** During the hearing I asked if you were inclined to grant an exemption to asbestos used by the chloralkali industry, which imports 95% of asbestos into the United States. You said that you would have to look into the issue. Now that you have had more

time to study the issue, are you going to exempt asbestos used by the chloralkali industry from regulation?

91. ***OPA:*** EPA has reduced climate change website access to at least 5,000 pages, possibly many more, of scientific, policy, and educational material paid for by taxpayer dollars over the past year. In the one example of content being partially returned to the website, all of the more than 200 climate-related webpages were omitted from what was previously a 380-page website titled "Climate and Energy Resources for State, Local, and Tribal Governments," which has now been renamed simply "Energy Resources for State, Local, and Tribal Governments." How do you justify such overt censorship of taxpayer-funded information that was created to help state, local, and tribal decision-makers protect the well-being of their constituents? Will you return this content to the EPA website so that the public can benefit from it again?

92. ***OEI:*** According to the Paperwork Reduction Act, 44 USC § 3506(d)(3), all agencies must "provide adequate notice when initiating, substantially modifying, or terminating significant information dissemination products." The news release announcing that the EPA was overhauling its website was published the same day that the EPA removed the vast majority of its climate change website, thousands of webpages -- the public did not have an opportunity to provide comment or express its concerns. How do you justify overtly disregarding this process and failing to notify the public?

93. ***OGC/OARM/OPA:*** While Dr. Michael Dourson was under consideration to be Assistant Administrator of the Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention (OCSPP), he was employed as a senior adviser at the EPA.
    a. What was Dr. Dourson's job title and type of appointment?
    b. Whom did he supervise?
    c. Did you delegate any duties of the OCSPP to him? If so, what were they?
    d. What projects did Dr. Dourson work on while at EPA and what was his role related to these projects?
    e. What monetary and non-monetary compensation did Dr. Douson receive while he was employed at EPA?
    f. Please provide Dr. Dourson's daily schedule while he was at EPA.

94. ***OAR:*** You claim that special interest groups have been circumventing the regulatory process through litigation, resulting in creation of regulation via consent decrees and settlement agreements. However, EPA has been making "policy decisions" of late that do just that--circumvent the rulemaking process. EPA's January 25 guidance allowing the downgrade of source status from "major" to "area" has a major impact on reporting and compliance requirements, yet this new benefit to industry did not undergo the required regulatory process under the Administrative Procedures Act.
    a. Please describe how EPA is increasing transparency and improving public engagement with respect to making the decision to downgrade source status for industries without a rulemaking, and how this is an improvement to public health and the environment.

95. ***OAR:*** Facilities will now have the ability to downgrade to an area source without needing to comply with maximum achievable control technology (MACT) standards, which require control efficiencies of 95% and higher. Please explain how the emissions reductions from MACT standards will be achieved when you are allowing sources to be recategorized as area sources.

96. ***OGC:*** Historically, environmental organizations have sued EPA due to lack of agency action on implementation of critical environmental laws, resulting in court decisions that force EPA to take action...or as you refer to it, sue and settle. What other courses of action can special interest groups pursue when EPA does not meet statutory deadlines?

97. ***OGC:*** In your Sue and Settle directive, you issued a memo to EPA managers (https://www.epa.gov/sites/production/files/2017-10/documents/signed_memorandum_in_support_of_consent_decree_and_settlement_agreement_oct162017.pdf) discussing how past practices of EPA have harmed the American public. In this memo, you say that EPA has met with outside groups behind closed door and excluded other interested stakeholders, essentially accusing EPA's Office of General Counsel of collusion. Is it your position that EPA lawyers are liable for collusion? If you believe that collusion has occurred, are you aware that many state bar associations consider collusion grounds for attorney discipline or even debarment? Was it your intention to endanger the status of all EPA attorneys?

98. ***OPA:*** It has been reported that the grant review process at EPA has been captured by political appointees.
    a. Can you please describe how the EPA is currently reviewing grants?
    b. Why is the EPA specifically targeting grants that are dealing with climate change and climate impacts?

Senator Sanders:

Climate Change

99. ***OPA:*** During a recent interview with KSNV TV, you stated:

> "Is (global climate change) an existential threat? Is it something that is unsustainable, or what kind of effect or harm is this going to have? I mean, we know that humans have most flourished during times of what? Warming trends. I think there's an assumption made that because the climate is warming, that (warming) is necessarily a bad thing. Do we really know what the ideal surface temperature should be in the year 2100? In the year 2018? I mean it's fairly arrogant for us to think that we know exactly what it should be in 2100."

The Trump Administration's *Climate Science Special Report*, the United Nation's Intergovernmental Panel on Climate Change's *Fifth Assessment Report*, and the Department of Defense's *National Security Implications of Climate-Related Risks and a Changing Climate* report all found with high confidence that global climate change and rising global temperatures are likely to cause rising sea levels and increase crop failures,

hunger, illness, and extreme weather. The Department of Defense's report identified these factors as clear risks to the United States' national security.

In January, the National Oceanic and Atmospheric Administration published a technical report that predicted that rising global temperatures could cause global mean sea levels to rise over ten feet by 2100. This sea level rise would displace more than 30 million Americans and mostly or completely cover Cape Canaveral, the U.S. Naval Academy, the Massachusetts Institute of Technology, the John F. Kennedy International and San Francisco International airports, and the Mar-a-Lago resort, among other prominent localities. Given the level of destruction anticipated, would you consider these outcomes to "necessarily be a bad thing"?

In January, the peer-reviewed journal, *Nature Climate Change*, published a report predicting that 260,000 people around the world will die annually by 2100 due to decreasing air quality and rising global temperatures. If global climate change and decreasing air quality were to cause this level of increase in annual deaths, would you consider that outcome to "necessarily be a bad thing"?

In 2012, the independent humanitarian group DARA estimated that between 2012 and 2030, 150,000 people around the world will die annually due to infections and 360,000 people will die annually due to hunger and malnutrition related to rising global temperatures. If a warming climate were to cause this type of increase in illness, would you consider that outcome to "necessarily be a bad thing"?

The Union of Concerned Scientists estimates that if global warming emissions continue to grow unabated, the annual economic impact of more severe hurricanes, residential real-estate losses to sea-level rise, and growing water and energy costs could reach 1.9% of the U.S. GDP by 2100. They also estimate that a sea-level rise of 13-20 inches by 2100 would threaten insured properties in U.S. Northeast coastal communities valued at $4.7 trillion. If a warming climate were to cause these types of economic impacts, would you consider that outcome to "necessarily be a bad thing"?

Lead

100. ***OW:*** You have stated that "[l]ead poisoning is an insidious menace that robs our children of their intellect and their future." This is especially true for children living in communities of color, who are most likely to suffer from lead exposure and poisoning. According to the Center for Disease Control, African American children are over three times as likely to have highly elevated blood-lead levels. African American and Latino communities are often more likely to live near active battery recyclers, industrial sites, or highways, and to live in older housing that are sources of high levels of lead. In addition, a 2012 study found that lead exposure resulted in greater cognitive detriment for children with a lower socioeconomic status. Scientists agree that there is absolutely no acceptable level of lead exposure for children.

Based on your own statement, will you commit to eradicating lead exposure for America's children? How will you work with other leaders in the Administration to ensure the safety of our children, including those in more vulnerable communities?

101. ***OW:*** In 2015, the Natural Resource Defense Council found that more than 18 million Americans were served by community water systems that had violated the EPA's Lead and Copper Rule, which limits the concentration of lead and copper in public drinking water. You estimated it would cost "as much as $30 billion or maybe upward of $50 billion" to replace all the lead service lines across the country, implying that this price tag is too high. However, Fitch Ratings, an independent credit rating agency, has estimated that the capital costs to replace these lines could be over $275 billion. Based on the discrepancy in these figures, please detail how you arrived at your estimate, and explain why it is so much lower than that of Fitch Ratings.

EPA Website

102. ***OPA:*** On April 28, 2017, the EPA removed its climate change website. To this day, the removed pages redirect to a notice stating, "we are currently updating our website to reflect EPA's priorities under the leadership of President Trump and Administrator Pruitt." The EPA did not announce the overhaul prior to its start date and has not yet provided a justification for the removals.

According to the Paperwork Reduction Act, all agencies must "provide adequate notice when initiating, substantially modifying, or terminating significant information dissemination products." The EPA's announcement regarding its website overhaul was published on the same day that the EPA removed the vast majority of its climate change website, and therefore the public did not have an opportunity to provide comment or express concerns.

Does the EPA generally take public comments into account when making these types of decisions?

Can you please explain how announcing an overhaul of the climate website on the same day changes were made constitutes "adequate notice" under the Paperwork Reduction Act?

103. ***OPA:*** On February 2, 2018, the Associated Press reported that internal EPA emails, released following a Freedom of Information Act request by the Environmental Defense Fund, show that you personally monitored efforts to overhaul the EPA's climate change website. One email from Lincoln Ferguson, an EPA senior advisor for public affairs, states:

> "How close are we to launching this on the website? The Administrator would like it to go up ASAP. He also has several other changes that need to take place."

Did the EPA, under your leadership, remove the content of the EPA's climate change website and replace the removed pages with a notice stating "this page is being updated

to reflect the agency's new direction under President Donald Trump and Administrator Scott Pruitt"?

Was this overhaul announced prior to its start date? If not, why not?
Please provide a specific time for the EPA's climate change website to come back online.

104. ***OAR/OPA:*** Did the EPA, under your leadership, remove web resources providing information about the benefits of the Clean Power Plan months before the proposed rulemaking to withdraw the rule?

If so, did the EPA remove website information regarding what was, at the time, current EPA policy before initiating the appropriate rulemaking process?

Renewable Energy

105. ***OPA:*** In October 2017, you said that if it were up to you, you would do away with the Renewable Electricity Production Tax Credit and the Investment Tax Credit for wind and solar. You stated:

> "I'd let (solar and wind) stand on their own and compete against coal and natural gas and other sources, and let utilities make real-time market decisions on those types of things as opposed to being propped up by tax incentives and other credits that occur, both in the federal and state level."

As you may know, the United States currently wastes billions of dollars each year subsidizing the fossil fuel industry. Since you believe energy tax credits should be eliminated to let technologies "stand on their own," do you also believe we should eliminate fossil fuel subsidies to let coal, oil and gas "stand on their own" as well? If so, what actions are you taking to eliminate the unfair subsidization of certain energy resources?

Senator Van Hollen:

106. ***OCSPP:*** You have noted repeatedly – more than a dozen times in your appearances before Congress and in your testimony for today– that EPA's only authority is the "rule of law" or "the authority given to it by Congress".

The updates to the Toxic Substances Control Act Congress enacted in 2016 directed EPA to assess the safety of new chemicals before they go onto the market. The law says that EPA, quote, "shall issue an order" regulating the chemical in order to protect against the danger the new chemical may pose.

On January 17th of this year, you told CBS News that EPA should not regulate new chemicals using orders even though the law clearly says otherwise. Your views appear to be in direct conflict with the law Congress wrote.

Mr. Pruitt, will you direct EPA staff to issue orders to regulate the safety of new chemicals under all circumstances in which the law says that orders are required?

107. ***OPA:*** I appreciated your recent announcement that that you have decided not to abandon proposed EPA oversight of the massive Pebble Mine, leaving restrictions in place while the Agency receives more information on the potential mine's impact on the region's world-class fisheries and natural resources. Given EPA's role in this process, would you say that EPA can contribute valuable feedback to the development of projects, be they energy, mining, or transportation? Given EPA's valuable feedback, would you object to efforts to roll back EPA's responsibilities to provide input on infrastructure projects?

Senator Wicker:

108. ***OAR:*** Do you support providing hardship exemptions from Renewable Fuel Volume Obligations (RVOs) for small refineries experiencing disproportionate economic impacts from high RIN prices?

Message

From: Glenn, Barbara [Glenn.Barbara@epa.gov]
Sent: 12/12/2017 4:47:50 PM
To: Bateson, Thomas [Bateson.Thomas@epa.gov]
CC: Kraft, Andrew [Kraft.Andrew@epa.gov]
Subject: formaldehyde and ML
Attachments: Mundt et al 2017_Eupub.pdf; AML analyses.docx; Pira_2014.pdf

Hi Tom,
I hope you are enjoying the SRA conference and you will be able to say goodbye to Ila in person!

I wanted to bring to your attention the review by Mundt accepted by Regulatory Toxicology and Pharmacology as there is a discussion about the literature on ML. A publication by Pira is described that I don't think we have reviewed (attached here). Mundt et al points out that there are six studies that conducted analyses of AML and it seems on its face that would be enough to synthesize. In our assessment we don't explain why we evaluated ML and not AML specifically. It seems that would be useful to do in the discussion of the specific diagnosis selected for the review. Here is that paragraph. Would you add a rationale for the level selected to review?

Also, I made a table of the six studies and added a few notes with questions that may come up.

Thanks for your help as we try to finish up.

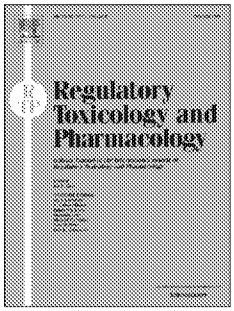
Regards, Barbara

Myeloid leukemia

Epidemiologic Evidence

The most specific classification of myeloid leukemia diagnosis that is commonly reported across the epidemiologic literature has been based on the first three digits of the Eighth or Ninth Revision of the ICD code (i.e., Myeloid Leukemia ICD-8/9: 205). For the purposes of this evaluation, cancer cases reported as monocytic leukemia or nonlymphocytic leukemia were included as myeloid leukemia. Evidence describing the association between formaldehyde exposure and the risk of myeloid leukemia was available from 12 epidemiologic papers reporting on 10 different study populations—three case-control studies {Talibov, 2014, 2799600;Hauptmann, 2009, 626498;Blair, 2001, 735839} and nine cohort studies {Coggon, 2014, 2337789;Meyers, 2013, 1998382;Saberi Hosnijeh, 2013, 2969929;Beane Freeman, 2009, 627726;Hayes, 1990, 626510;Ott, 1989, 1010430;Stroup, 1986, 626848;Walrath, 1983, 21345;Walrath, 1984, 626708}. {Hauptmann, 2009, 626498@@author-year} combined the study populations from {Hayes, 1990, 626510@@author-year} with those from Walrath and Fraumeni {, 1983, 21345;, 1984, 626708} and reconstructed individual exposure estimates. {Checkoway, 2015, 2965827@@author-year} reanalyzed {Beane Freeman, 2009, 627726@@author-year} with different definition of the exposure categories and presented results for specific sub-types of myelois leukemia. These are the only formaldehyde studies that specifically evaluated the risk of myeloid leukemia. The outcome-specific evaluations of confidence in the reported effect estimate of an association from each study are provided in Appendix A.5.9, Tables A-96 and A-97 and the confidence conclusions are provided in the evidence table for myeloid leukemia (see Table 1-67) following the causal evaluation.

Accepted Manuscript



Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity

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Six years after the NRC Review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity

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Abstract

Shortly after the International Agency for Research on Cancer (IARC) determined that formaldehyde causes leukemia, the United States Environmental Protection Agency (EPA) released its Draft IRIS Toxicological Review of Formaldehyde, also concluding that formaldehyde causes leukemia. Peer review of the EPA Draft IRIS Assessment by a National Academy of Science committee noted that "causal determinations are not supported by the narrative provided in the draft" {NRC 2011}. They offered recommendations for improving the IRIS review and identified several important research gaps. Over the six years since the NRC peer review, significant new science has been published. We identify and summarize key NRC recommendations and map them to this new science, including extended analysis of epidemiological studies, updates of earlier occupational cohort studies, toxicological experiments using a sensitive mouse strain, mechanistic studies examining the role of exogenous versus endogenous formaldehyde in bone marrow, and several critical reviews. With few exceptions, new findings are consistently negative, and integration of all available evidence challenges the earlier conclusions that formaldehyde causes leukemia. Given formaldehyde's commercial importance, environmental ubiquity and endogenous production, accurate hazard classification and risk evaluation of whether exposure to formaldehyde from occupational, residential and consumer products causes leukemia are critical.

Key Words: Regulatory science, hazard evaluation, evidence integration, epidemiology, toxicology, mechanistic studies

1.0 Introduction

Classification and regulation of human carcinogens is a key component to the protection and improvement of public health. However, proper regulation of industrial chemicals hinges on both valid hazard identification and quantitative risk assessment. Increasingly, hazard identification – at least where adequate scientific evidence is available – draws on critically assessing and integrating evidence across lines of inquiry including animal and human toxicology (e.g., pharmacokinetic, mechanistic studies) and epidemiology. Quantitative risk assessment requires reasonably accurate characterization of exposures, which is complicated, especially where historical measures are sparse or do not exist. Where adequate evidence from some or all of these is lacking, and where important uncertainties remain, policy-driven approaches favoring precaution are warranted. On the other hand, as evidence accumulates, more science-focused methods can be employed, reducing uncertainties, leading to sounder conclusions. Nevertheless, confident conclusions are sometimes drawn prematurely, as discussed in this commentary. Recent evaluations of formaldehyde, coupled with improved critical review and evidence integration expectations and new, more focused scientific evaluations, illustrate the dynamic nature of scientific inquiry and the need for parallel refinement of hazard characterization, and subsequently, stronger risk assessment.

In this paper, we illustrate the evolution of new scientific evidence on formaldehyde as a potential human leukemogen. The impetus for the new science summarized below is derived from the International Agency for Research on Cancer's (IARC) 2009 classification of formaldehyde as a known cause of leukemia in Monograph 100F (Baan, et al. 2009; IARC, 2012), the US Environmental Protection Agency's (EPA's) similar classification in a Draft IRIS (Integrated Risk Information System) Toxicological Review of Formaldehyde – Inhalation Assessment (hereafter referred to as the "Draft IRIS Assessment") (EPA 2010), and the criticisms and recommendations presented in two National Academy of Science (NAS), National Research Council (NRC) expert reviews – one on the Draft IRIS Assessment and one on

the IRIS process itself (EPA 2010; IARC 2012; NRC 2011; NRC 2014a). Various organizations and agencies have contributed to or sponsored the new science, including governments and universities, as well as industry. In revising and finalizing the Draft IRIS Assessment (EPA 2010), EPA now has the opportunity to incorporate the new evidence in addressing many of the issues raised by the NRC reviews.

2.0 Formaldehyde Cancer Hazard Evaluation

The carcinogenicity of formaldehyde has been evaluated by several agencies since the early 1980s, including the IARC, the National Toxicology Program (NTP) of the National Institute for Environmental Health Sciences (NIEHS), the EPA, and most recently, the Committee for Risk Assessment (RAC) of the European Chemicals Agency (ECHA) and the Scientific Committee on Occupational Exposure Limits (SCOEL) of the European Commission (table 1). Except for the RAC review (RAC 2012) and the SCOEL review (Bolt et al. 2016) , which reclassified formaldehyde as a Carcinogen Category 1B (i.e., presumed to have carcinogenic potential for humans) and a Category C carcinogen (i.e., genotoxic carcinogen with a mode of action based threshold), respectively, these reviews classified formaldehyde as a known human carcinogen, primarily based on NPC but also on lymphohematopoietic malignancies (LHM) as a group and/or all leukemias as a group, and all myeloid leukemias (ML) as a group (EPA 2010; IARC 2012; NTP 2011). Differences between NTP (2012) and EPA draft classifications (final version of the EPA review is pending) have been highlighted by Rhomberg (2015a) and differences between the IARC (2012) and the RAC (RAC ECHA, 2012) evaluations have been discussed by Marsh et al (2014).

The reviews by authoritative bodies acknowledged that hazard identification for formaldehyde was not straightforward, especially with respect to possible leukemogenicity, in part due to its endogenous production and high reactivity. This prompted closer scrutiny regarding the methods used to critically evaluate the strength and quality of scientific studies, and ultimately, how best to integrate evidence across lines of inquiry such as animal, mechanistic and epidemiological evaluations.

IARC first classified formaldehyde as "carcinogenic to humans" (i.e., Group 1) in 2005 (Cogliano, et al. 2005; IARC 2006), revising the previous evaluation in 1995 that formaldehyde is "probably carcinogenic to humans" (i.e., Group 2A) (Table 1). The 2005 evaluation concluded that formaldehyde causes NPC, based primarily on results from animal studies, with additional evidence from "the largest and most informative cohort study of industrial workers" (i.e., Hauptmann, et al. 2004, Cogliano et al., 2005). Results from animal studies demonstrated that formaldehyde in direct contact with nasal passage tissues induced tumors at formaldehyde concentrations > 2 ppm as summarized by Nielsen and Wolkoff (2013) and later by Nielsen, et al. (2017). This was considered consistent with formaldehyde's demonstrated genotoxicity, and with the "sufficient epidemiological evidence that formaldehyde causes nasopharyngeal cancer in humans" (IARC 2006).

IARC (2012) concluded that formaldehyde also causes leukemia, and in particular ML, although that Working Group noted that it was a "small majority" who found the evidence as sufficient. Neither Hauptmann, et al. (2003) nor the subsequently updated study (Beane Freeman, et al. 2009) published results specifically for acute myeloid leukemia (AML). The Working Group noted a study reporting aneuploidy in the blood of exposed workers (Zhang, et al. 2010), recently accepted for publication, provided supporting data, with the caveat that the study needed to be replicated (IARC 2012). Indeed, proper replication of this study is still needed, because the study protocol was not consistent with adequate cell counting standards, including the authors' earlier descriptions of the OctoChrome FISH method (Zhang, et al. 2005; Zhang, et al. 2011) and other standards (American Society of Medical Genetics, 2006). One particular challenge is that occupational exposure limits in North America, Europe and in many countries around the world protect workers from the levels of occupational formaldehyde exposures that were studied by Zhang, et al. (2010) in China making replication of the study logistically difficult. Proper replication of this study also will require use of methods to successfully distinguish

between aneuploidy arising *in vivo* from aneuploidy that arises during the period of *in vitro* culture, as discussed in section 3.3.3 below.

Following the IARC review and classification, the National Toxicology Program (NTP) concluded that formaldehyde causes nasopharyngeal cancer and myeloid leukemia in the 12th Report on Carcinogens (NTP 2012) (Table 1). The 12th RoC stated "The most informative studies for evaluation of the risk of ML are the large cohort studies of industrial workers (the NCI, NIOSH, and British cohorts) and the NCI nested case-control study[1] of lymphohematopoietic cancer in embalmers" and specifically that "Three of these four studies found elevated risks of myeloid leukemia among individuals with high exposure to formaldehyde, as well as positive exposure-response relationships". However, the NTP also noted "In the large cohort of British chemical workers, no increased risk of leukemia was found for formaldehyde exposure" and that in the only case-control study examining ML (Blair, et al. 2000) "an excess risk was found for chronic (but not acute) myeloid leukemia" (NTP, RoC, 12th edition, "Formaldehyde", p.3).

2.1 Environmental Protection Agency Integrated Risk Assessment Program (IRIS)

Formaldehyde had been classified by the EPA as a "probable" human carcinogen (Group 1B) in 1991 (Table 1). An updated assessment for public review and comment was first released in June 2010, 12 years after the EPA announced the re-evaluation, and the draft assessment reported that formaldehyde causes NPC, nasal and paranasal cancer, lymphohematopoietic cancers, all leukemias, and ML (Table 1). The EPA (2010) also derived a draft inhalation unit risk (IUR) value of 8.1×10^{-2} per ppm (6.6×10^{-5} per $\mu g/m^3$)[2] based on the upper bound on the sum of the risk estimates for NPC, Hodgkin lymphoma, and

[1] This study technically is not a "nested case-control study" but rather a pooled reanalysis of death certificate data from several published proportionate mortality ratio (PMR) analyses, using a case-control approach. Thus, it carries the same limitations of death certificate analyses performed outside of a well enumerated cohort, and therefore is not "nested" in any true cohort that could be accurately enumerated.

[2] This is 15 times higher than the inhalation unit risk (IUR) derived by EPA for vinyl chloride (4.4×10^{-6} per $\mu g/m^3$) (EPA 2000, page 50), a chemical for which the evidence clearly supports a causal association between exposure and effects in both animals and humans.

leukemia (combined risks) based on part of the results reported in Beane Freeman et al. (2009). For rationale, the EPA said the classification "is supported by cohort analyses of embalmers, pathologists and anatomists (Hall, et al. 1991; Hayes, et al. 1990; Levine, et al. 1984; Matanoski 1989; Stroup, et al. 1986; Walrath, Fraumeni 1983, 1984; Yuan, et al.2007)" despite the observation that ". . . SMR analyses of the large industrial cohorts do not indicate a similar association (Beane Freeman, et al. 2009; Coggon, et al. 2003; Pinkerton, et al. 2004)" (page 4-180). The EPA also cited three meta-analyses (Bosetti, et al. 2008; Collins and Lineker 2004; Zhang et al. 2009) that largely included the same studies as providing additional evidence. Repeatedly reporting the same results, however, does not constitute independent or additional evidence. Similarly, all meta-analyses included earlier versions of the NCI cohort workers and embalmers studies and therefore, they, too, are redundant with the meta-analyses.

The conclusions in the EPA Draft specific to myeloid leukemia are as follows:

> "Given the consistency of the positive associations for formaldehyde with myeloid leukemia cancer mortality across five of the six studies (Hauptmann, et al. 2009; Hayes, et al. 1990; Pinkerton, et al. 2004; Stroup, et al. 1986; Walrath and Fraumeni 1984; Walrath and Fraumeni, 1983; but not Beane Freeman, et al. 2009) , the statistically significant meta-analysis by Zhang et al. (2009) and the convincing results from Hauptmann et al. (2009), the human epidemiologic evidence is sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from myeloid leukemia." (EPA 2010) (pages 4-184, 4-185)

Again, because of the significant overlap between Hauptmann et al. (2009) and the three PMR studies of funeral directors and embalmers (Hayes, et al. 1990; Walrath, Fraumeni 1983, 1984) these overlapping reports do not constitute independent evidence or consistency across studies. Hauptmann et al. (2009) has been judged to have severe methodological flaws (Cole et al. 2010a; b); as such, these results are not convincing. Separately, the Zhang et al. (2009) meta-analysis combined different exposure metrics (peak, average intensity, cumulative exposure, duration), and thus, the exposure metrics were not comparable across studies. A more methodologically rigorous approach would be to perform meta-analyses for similar exposure metrics, that is, a meta-RR for cumulative exposure, meta-RR for average

exposure, meta-RR for duration of exposure (only one study reported results in relation to peak exposure, precluding a meta-analysis for peak exposure). As such, the Zhang (2009) meta-analysis results are difficult to interpret and methodologically flawed. Finally, combining data in a meta-analyses does not overcome any systematic biases in the underlying studies (Greenland and Longnecker, 1992).

2.2 National Academies Peer-Review Process

The NRC of the NAS, at the request of the EPA, formed an expert Committee to perform the peer-review of the EPA Draft. Following a series of meetings during the second half of 2010, the NRC issued the final report on April 8, 2011 (NRC 2011) as a pre-publication copy. The Committee identified numerous constructive criticisms and data gaps, and provided recommendations for improving IRIS reviews in general (NRC 2011). Though not directly charged to evaluate the EPA Draft conclusions, the peer review raised important questions regarding the underlying methods giving rise to several conclusions, including the basic causal conclusions:

> "EPA evaluated the evidence of a causal relationship between formaldehyde exposure and several groupings of LHP cancers—"all LHP cancers," "all leukemias," and "myeloid leukemias." The committee does not support the grouping of "all LHP cancers" because it combines many diverse cancers that are not closely related in etiology and cells of origin. The committee recommends that EPA focus on the most specific diagnoses available in the epidemiologic data, such as acute myeloblastic leukemia, chronic lymphocytic leukemia, and specific lymphomas." (NRC 2011, Summary, page 11)

The Committee concluded that EPA's claims that formaldehyde causes leukemia, ML or related hematopoietic cancers were not supported in EPA's assessment, appeared to be subjective in nature, and that no clear scientific framework had been applied by EPA in reaching that conclusion (NRC 2011). The absence of such a framework was judged by the committee as problematic:

> "As with the respiratory tract cancers, the draft IRIS assessment does not provide a clear framework for causal determinations. As a result, the conclusions appear to be based on a subjective view of the overall data, and the absence of a causal framework for these cancers is particularly problematic given the inconsistencies in the epidemiologic data, the weak animal data, and the lack of mechanistic data. Although EPA provided an exhaustive description of the studies and speculated extensively on possible modes of

> action, the causal determinations are not supported by the narrative provided in the draft IRIS assessment. Accordingly, the committee recommends that EPA revisit arguments that support determinations of causality for specific LHP cancers and in so doing include detailed descriptions of the criteria that were used to weigh evidence and assess causality. That will add needed transparency and validity to its conclusions." (page 11, NRC 2011)

The NRC further pointed out that that EPA (2010) conclusion that formaldehyde causes ML was based primarily on selected epidemiological studies, and other streams of evidence (animal, mode of action) were not considered beyond studies conducted by Zhang et al. (2009, 2010).

In the 7th and final chapter of its review, entitled, "A Roadmap for Revision," the NRC provided recommendations in two categories: "Critical Revisions of the Current Draft IRIS Assessment of Formaldehyde," and "Future Assessments and the IRIS Process" (NRC 2011). NRC (2011) specifically identified the systematic review standards adopted by the Institute of Medicine (IOM), as being appropriate for such an analysis (IOM 2011).

Following the release of the NRC (2011) peer review, Congress issued House Report No. 112-151, and directed EPA to incorporate recommendations of Chapter 7 of the NRC (2011) report into the IRIS process. In 2014, NRC released an additional report on the IRIS process (NRC 2014a), and emphasized the importance of evidence integration for hazard identification, in which studies of higher quality and low risk of bias are given greater weight in drawing conclusions regarding causality.

As part of their response to the NRC reviews, the EPA convened a state-of-the-science workshop on formaldehyde on April 30 and May 1, 2014 in Arlington, Virginia. This workshop focused on three themes:

- Evidence pertaining to the influence of formaldehyde that is produced endogenously (by the body during normal biological processes) on the toxicity of inhaled formaldehyde, and implications for the health assessment;
- Mechanistic evidence relevant to formaldehyde inhalation exposure and lymphohematopoietic cancers (leukemia and lymphomas); and

- Epidemiological research examining the potential association between formaldehyde exposure and lymphohematopoietic cancers (leukemia and lymphomas).
  (From: https://www.epa.gov/iris/formaldehyde-workshop)

A second workshop was announced at the meeting but never was convened. Since then, House Report No. 114-632 (page 57-59) and Senate Report No. 114-281 (page 62) have requested the allocation of funds for NRC to peer review the revised IRIS Toxicological Review of Formaldehyde, to ensure that recommendations raised by the NRC (2011) were implemented.

3.0 New studies published since the 2011 NRC Peer Review of the Draft IRIS Assessment

Numerous studies and updated analyses have been published since the 2011 NRC Peer Review of the Draft IRIS Assessment, the findings of which, at least in part, fill many of the "data gaps" and address several key methodological issues highlighted in the NRC Committee recommendations (2011). Below we summarize this new research, organized around the data streams (e.g., epidemiological, toxicological, and mode of action) for evidence integration and quantification of potential leukemia risks, specifically responsive to the following NRC recommendations (2011) (page reference provided):

- ***Epidemiological Evidence***
  - Discussion of the specific strengths, weaknesses and inconsistencies in several key studies, as the draft IRIS assessment relies solely on epidemiologic studies to determine causality. (*p.113*)
  - Clarification of the basis of its interpretations of the results regarding the various dose metrics (peak versus cumulative) and the various LHP cancers. (*p.113*)
  - Evaluation of the most specific diagnoses available in the epidemiologic data (i.e., acute myeloblastic leukemia, chronic lymphocytic leukemia, and other specific lymphomas). (*p. 113*)
- ***Toxicological Evidence***
  - Paucity of evidence of formaldehyde-induced LHP cancers in animal models. EPA's unpublished re-analysis of the Battelle chronic experiments in mice and rats (Battelle Columbus Laboratories 1981), although intriguing, provides the only positive findings and thus does not contribute to the weight of evidence of causality. (*p.110*)

- ***Mode of Action Evidence***
  - Improving the understanding of when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations. (*p. 58*)
  - Reconciliation of divergent statements regarding systemic delivery of formaldehyde, *(p.59)* as direct evidence of systemic delivery of formaldehyde is generally lacking. (*p.5*)
  - Data are insufficient to conclude definitively that formaldehyde is causing cytogenetic effects at distant sites. *(p. 5)*

- ***Dose-Response Assessment***
  - Independent analyses of the dose-response models to confirm the degree to which the models fit the data appropriately. *(p. 14)*
  - Consideration of the use of alternative extrapolation models for the analysis of the cancer data. *(p.14)*
  - Further justification of the selection and use of the NCI cohort (Beane Freeman, et al. 2009) for calculation of unit risk because the cumulative exposure metric (used in the calculation of unit risk) was not related to leukemia risk in the NCI cohort. (*p.112*)

- ***Methods for Evidence Integration***
  - Development of an approach to weight of evidence that includes "a single integrative step after assessing all of the individual lines of evidence". Although a synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and how that evidence was integrated into a final conclusion are not apparent in the draft assessment and should be made clear in the final version. *(p. 113)*

A summary of each of these recommendations and data gaps, along with the new science that has been conducted to address them is provided in Table 2 and discussed in the following sections.

3.1 Epidemiological Evidence

The NRC Peer Review called attention to the EPA's sole reliance on epidemiological studies to determine causality, rather than integrating epidemiology data with the toxicological and mechanistic evidence. When inferring causation from epidemiology studies, the evidence is critically assessed and synthesized across a body of individual studies, with greater weight assigned to studies of higher quality (rather than assigning equal weight to each). Better epidemiological studies are those that implement individual level exposure data, and minimize the potential for systematic bias and confounding. The ascertainment of outcome and analysis using accurate (and specific) diagnosis are also critical in the

causal evaluation. NRC noted that the grouping of "all LHPs" comprises 14 biologically distinct diagnoses in humans and should not be used in determinations of causality. There is some evidence that these diseases may originate from the same stem cell line (Gluzman, et al. 2015; Goldstein 2010) and could therefore arise from direct effects on these cells. There are no studies, however, that demonstrate an effect on these stem cells following exposure to formaldehyde. The largest population of these stem cells would be found in the bone marrow, and, based on the available evidence, inhaled formaldehyde appears incapable of reaching the bone marrow (see Section 3.3.2). The affected cells would need to be circulating stem cells that encounter formaldehyde at the portal of entry (i.e., the nose or upper airways) and then return to the bone marrow.

After the NRC Peer Review was published, Checkoway et al. (2012) critically reviewed the epidemiological evidence and reported inconsistent and sporadic associations between formaldehyde exposure and various specific LHM, including ML and only a few considering AML specifically. Since the critical review (Checkoway, et al. 2012), several additional epidemiological studies have been published that provide insights on formaldehyde exposure and AML risk and address other specific issues raised by the 2011 NRC Peer Review. The key strengths and limitations of these studies are highlighted below.

3.1.1 Key studies and their strengths and limitations

Since the update of mortality in the US formaldehyde users and producers cohort (Beane Freeman, et al. 2009), two other large industrywide cohort mortality studies have been updated: the NIOSH garment workers (Meyers, et al. 2013) and the UK industry-wide formaldehyde producers and users (Coggon, et al. 2014). In addition, a large population-registry-based case-control study of incident AML cases in the Nordic countries, a small occupational study in Italy and a large multicenter European study of

occupational exposures in a cohort established to study nutritional and metabolic risk factors in cancer risks have been published (Pira, et al. 2014; Saberi Hosnijeh, et al. 2013; Talibov, et al. 2014).

NIOSH cohort study of garment workers

Meyers et al. (2013) updated mortality from 1960 through 2008 for 11,043 US garment workers exposed to formaldehyde who worked for at least three months between 1955 and 1983 at three US factories. A total of 36 leukemia deaths was reported (SMR=1.04, 95% CI 0.73 - 1.44, compared to US mortality rates), of which 21 were ML (14 AML, 5 chronic myeloid leukemia (CML), 2 other and unspecified ML). Although this study did not link quantitative estimates of formaldehyde exposure to study subjects, an industrial hygiene survey during the early 1980s reported that formaldehyde concentrations were similar across all departments and facilities, and the overall geometric mean was 0.15 ppm with a geometric standard deviation of 1.90 (Stayner, et al. 1988). The formaldehyde resins used to treat permanent press fabrics had been reformulated over time, and as a result, the formaldehyde concentrations measured in the early 1980s were believed to be lower than the approximately 4 ppm estimated by NRC for years prior to 1970 (NRC 2014b). Meyers et al. (2013) reported an SMR for AML of 1.22 (95% CI 0.67 - 2.05), noting that they "continue to see limited evidence of an association between formaldehyde and leukemia" and that "the extended follow-up did not strengthen previously observed associations." All 14 AML occurred 20 or more years after first exposure to formaldehyde. The NIOSH study is a large cohort with adequate follow up but limited industrial hygiene measurements of historical formaldehyde concentrations, as most were first exposed prior to 1970. Therefore, the study did not assign individual estimates of cumulative or peak exposure, and analyses for mortality due to various LHM including AML were performed by duration of exposure. Information on smoking was also lacking.

Registry-based case control study of AML in Nordic countries

Talibov et al. (2014) analyzed 15,332 incident cases of AML diagnosed in Finland, Norway, Sweden, and Iceland from 1961 to 2005. The investigators matched 76,660 controls by year of birth, sex, and country. Job titles and dates of assignment were linked to a job-exposure matrix (JEM) to estimate quantitative exposure to 26 workplace agents, including formaldehyde. No association was seen between risk of AML and increasing cumulative exposure to formaldehyde, after adjusting for exposure to solvents (aliphatic and alicyclic hydrocarbon solvents, benzene, toluene, trichloroethylene, methylene chloride, perchloroethylene, other organic solvents) and radiation (hazard ratio (HR) 0.89, 95% CI 0.81 - 0.97 for workers exposed to ≤0.171 ppm-years; HR 0.92, 95% CI 0.83 -1.03 for workers exposed to 0.171 - 1.6 ppm-yrs, and HR 1.17, 95% CI 0.91 - 1.51 for > 1.6 ppm-years, compared to workers not exposed to formaldehyde). The strengths of this study were its exposure assessment based on a validated job exposure matrix (JEM) and the comprehensive ascertainment of incident (not mortality) AML cases, resulting in high statistical power to detect increased risks and the ability to consider and control for other possible leukemogens. One major limitation is the lack of data on smoking, which also is known to cause leukemia. This study failed to find an association between benzene and AML; however, risk of AML may be limited to very high concentrations that historically occurred only in a few occupational settings, e.g., the rubber hydrochloride industry (Infante, et al. 1977; Schnatter, et al. 2012).

European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study

Saberi Hosnijeh et al. (2013) followed 241,465 subjects from 1992 through 2010 for a prospective study of lymphoid and myeloid leukemia risk in relation to occupation, nutrition and metabolic risk factors. The European Prospective Investigation into Cancer (EPIC) investigators studied occupational risk factors among 477 incident leukemia cases (201 ML, including 113 AML, and 237 lymphoid leukemia) in France, Oxford (UK), the Netherlands, Sweden, Norway, and Italy (Saberi Hosnijeh, et al. 2013). Occupational

exposures were estimated using a general population job exposure matrix that classified occupational codes of study subjects into categories of high, low, and no exposure for 11 specific agents (e.g., benzene, trichloroethylene) or groups of agents (e.g., pesticides, chlorinated solvents). However, the authors note that work histories were missing on a large number of cohort member, and these individuals had to be excluded, and lacking detail on others but that these effects would be non-differential, attenuating risk estimates. On the other hand, this is one of the few studies examining specific subtypes of leukemia adjusted for smoking (as well as alcohol consumption, age at recruitment, sex, and country). AML risk was not increased among the low formaldehyde exposure group (HR 1.01, 95% CI 0.65 - 1.57) after adjusting for sex, smoking status, alcohol intake, age at recruitment and country, and no AML cases occurred among individuals in the high-exposure category. An HR for chronic lymphocytic leukemia of 1.45 (95% CI 0.46 - 4.56) was reported among those with high exposure to formaldehyde, but this was based on 3 or fewer cases. ML risks were increased among those employed in chemical laboratories and shoe and leather workers, and weakly increased among those exposed to benzene but not those exposed to ionizing radiation (Saberi Hosnijeh et al. 2013).

UK formaldehyde users and producers cohort study

Coggon et al. (2014) updated mortality through 2012 for the UK cohort of 14,008 formaldehyde users and producers; however, the analysis grouped all ML and did not analyze AML mortality separately. Similar to other large industrial cohorts (Beane Freeman, et al. 2009; Meyers, et al. 2013), industrial hygiene measurements were not available in the early years and investigators estimated averages for job titles based on irritant symptoms and later measurements. Exposures were estimated to range from background (< 0.1 ppm), low exposure (0.1 - 0.5 ppm), moderate exposure (0.6 - 2.0 ppm) and high exposure (> 2 ppm). These exposure categories were similar to those estimated by Stewart et al. (1986) and applied in Beane Freeman et al. (2009). Moreover, a larger proportion (and greater number) of the

UK cohort was exposed to high concentrations of formaldehyde (approximately 18% of the cohort) than the US cohort (approximately 4% of the cohort). Coggon et al. 2014 reported no increased mortality from ML (SMR 1.16, 95% CI 0.60 -2.20 for background exposure; SMR=1.46, 95% CI 0.84 - 2.36 for low/moderate exposure; and SMR 0.93, 95% CI 0.450 -1.82 for high exposure). In a nested case-control analysis of 45 ML (diagnosis from underlying or contributing cause of death or as a cancer registration) and 450 controls matched on factory and age, no significantly increased risk of leukemia was seen. Although ML risk was non-statistically significantly increased among workers exposed to high concentrations for < 1 year (OR=1.77, 95% CI 0.45 - 7.03), workers exposed to high concentrations ≥ 1 year showed no increased risk (OR 0.96, 95% CI 0.24 - 3.82) (Coggon, et al. 2014).

Extended analysis of the NCI cohort study to evaluate specific types of myeloid leukemia

Checkoway et al. (2015) obtained the data from the NCI formaldehyde industrial workers cohort to further investigate specific types of leukemias, including AML (which had never been reported for this cohort), as well as performing an alternative analysis of peak exposure. The investigators reported that AML mortality was unrelated to cumulative exposure or peak exposure. Twelve of 34 AML deaths and 6 of 13 CML deaths occurred among study subjects with less than one year of employment. For workers employed at least one year, the risk of AML was highest (but not statistically significant) among workers with peak exposures of ≥2.0 to <4 ppm (HR 1.78, 95% CI 0.61-5.25) and no trend was seen with increasing category of peak exposure (p for trend 0.37). In contrast, CML risks were greater although the estimates were imprecise (HR 4.83, 95% CI 0.64-36.42 for peak exposure ≥2.0 to <4 ppm based on 2 CML deaths and HR 5.32, 95% CI 0.81-34.90 for peak exposure ≥4 ppm based on 2 CML deaths).

3.1.2 Synthesis of epidemiology studies: Exposure assessment issues identified by NRC

One of the major issues highlighted by the NRC peer review is that one exposure metric (peak exposure) was used to determine causality in the draft IRIS assessment, while a different exposure metric (cumulative exposure) was used for the dose-response evaluation to calculate an inhalation unit risk. The NRC (2011) review of the Draft IRIS Assessment stated "the reliance on the peak exposure metric to determine causality rather than the more conventional dose metric of cumulative exposure should be further justified particularly in the absence of established modes of action" [p.112]. NRC further elaborated:

> "In the absence of evidence regarding exposure-disease mechanisms, as in the case of formaldehyde and LHP cancers, cumulative exposure is typically the default dose metric applied in epidemiologic analyses and risk assessment. But the most significant results were found for peak exposures, which have the greatest associated uncertainty. In view of the importance of this study, EPA should clarify the basis of its interpretations of the results regarding the various dose metrics and the various LHP cancers. Despite those concerns, the committee agrees that the NCI study is the most appropriate available to carry forward for calculation of the unit risk." (pp. 112-113)

The NRC recommended that the quality of exposure assessment relied upon in epidemiological evaluations should be explicitly evaluated when weighting and synthesizing epidemiological evidence. Where known causal relationships have been observed, exposure-response relationships often are seen with various exposure metrics, with stronger associations seen when more relevant metrics and exposure time windows are examined. Results such as those reported by Beane Freeman et al. (2009) are a good example of conflicting findings: the conventional exposure metric, cumulative exposure, demonstrated no association with risk of ML, whereas a surrogate of 'peak' exposure suggested one (Beane Freeman 2009). When evaluating differences between cumulative exposure and peak exposure, and comparing risks associated with these, several differences should be highlighted.

NCI investigators (Beane Freeman, et al. 2009; Blair, et al. 1986; Hauptmann 2003) defined peak exposure as the maximum peak, and the NCI investigators substituted the time-weighted average (TWA) for jobs without assigned peak exposures (Stewart, et al. 1986). The authors reported a significant test

for trend between peak formaldehyde exposure and leukemia, but only when unexposed subjects were included. Increased risk was not seen for higher peak exposure categories (2.0 to <4.0 ppm, or ≥ 4.0 ppm) when compared to the lower peak category (>0 to <2.0 ppm). No association was reported with frequency of peak exposure, average intensity of exposure or with cumulative exposure to formaldehyde ("There was little evidence among formaldehyde workers of association for any lymphohematopoietic malignancy (LHM) with average intensity or cumulative exposure."). In fact, a 10% deficit of ML deaths (acute and chronic types combined) was reported when compared to US population mortality rates. In an internal analysis, Beane Freeman et al. (2009) reported that ML deaths were not associated with the number or frequency of peaks. If there were a true association between peak exposure and leukemia, one would expect to see an association with number of peaks and not only ever having a (perhaps a single) peak exposure. Hauptmann et al. (2003) acknowledge that "no measurements of peak exposure were available in this study. Peak exposures were therefore estimated by an industrial hygienist from knowledge of the job tasks and a comparison with the 8-hour time-weighted average" (Hauptmann et al. 2003, p. 1616; Stewart, et al. 1986). Stewart et al. (1986) reported that the exposure reconstruction included rating confidence (i.e., confident, less confident, not confident) in the exposure estimate; however, the "confidence" category appeared to apply to the "rank" exposure and not the "peak exposure." For example, if an IH specified "not confident" for an average exposure estimate, it is not clear how or if this information applied to the estimate of peak exposure (categorized during data collection as 1 = none, 2 = 0.1 - 0.5, 3 = 0.51 - 2.0, 4 = 2.1-4.0, 5 = > 4.0, 9 = unknown) (Stewart, et al. 1986).

In extended analyses of the NCI cohort study, Checkoway et al. (2015) refined the classification of peak exposure. Workers who did not work in jobs identified as likely having peak exposures were classified as not peak-exposed, and became the referent group. A total of 3,478 cohort members were classified as having worked in jobs with estimated peak exposure of 2-<4 ppm, and 2,907 worked in jobs with

estimated peak exposure of ≥4 ppm. Analysis by ML subtype (i.e., AML and CML deaths, separately) found no association between peak exposure and AML mortality (HR 1.71, 95% CI 0.72 - 4.07 and HR 1.43, 95% CI 0.56 - 3.63, respectively) (Checkoway, et al. 2015). However, 13 of the 34 AML deaths were classified as having worked in jobs likely having peak exposure >2.0 ppm, only 4 of which worked in these jobs within the 20 years preceding their AML death (i.e., latest exposure), and only one occurred (similar to the number expected) within the typical AML latency window of 2 to 15 years. Upon fuller analyses of these data, Checkoway et al. (2015) subsequently found that only a third of all the AML deaths were among cohort members assigned to categories with any peak exposure (i.e., >2.0 ppm), nearly all of whom had their last peak exposure more than 20 years earlier, well outside of the maximum latency window.

Coggon et al. (2014) also reported that limited IH data were available for the UK formaldehyde users and producers cohort, preventing the derivation of quantitative metrics. Nevertheless, the investigators expressed high confidence that the high exposure category corresponded to average concentrations of at least 2 ppm. Industrial hygiene data also were limited in the US NCI industrial workers study, although the investigators used them as part of a detailed exposure reconstruction using best practices for such a reconstruction at the time. Stewart, et al. (1986) reported that historical exposure levels were estimated because most companies did not begin sampling until the mid-1970's: they also monitored "present day" (i.e., early 1980's) operations to help extrapolate historical exposures. The NCI investigators relied up exposure rank (six levels of TWA): trace, < 0.1 ppm, 0.1 - 0.5 ppm, 0.51- 2.0 ppm and > 2 ppm.

One criticism leveled at the UK worker cohort study (Acheson, et al. 1984; Coggon, et al. 2003, 2014; Gardner, et al. 1993) was that the "authors reported a concern about the quality of data when they made exposure assignments" (NRC 2014b). This criticism seems to stem from the appropriate identification and discussion of study limitations by earlier UK investigators: Gardner et al. (1993)

reported "when jobs were being placed into qualitative categories of exposure in the British study, some disagreement occurred as to which of two adjacent grades was most appropriate-for example, high or moderate? To achieve consistency across all the factories, the higher of the two was always used. It is not clear how differences were resolved in the United States study." Thus, there are no essential differences in the approach used by the UK investigators and the US investigators: both studies reported that limited data were available on quantitative exposure measures using existing industrial hygiene data (from the 1980s); both classifications allowed for the consideration of changes in processes and exposure controls during the period of the study; and both used ranked categories of exposure, developed before the estimation process, based somewhat on subjective sensory experiences encountered in the job (e.g., odor occasionally present), and both used eye irritation and odor throughout the day to identify the highest intensity of exposure jobs (Acheson, et al. 1984; Stewart, et al. 1986).

Ultimately, the Beane Freeman et al. (2009) study alone does not (and cannot) provide reliable support for a conclusion that peak formaldehyde exposure causes ML or AML, especially considering the absence of peak measurement data in the US study, the results of the re-analysis by Checkoway et al. (2015), and the updated results from the UK study (Coggon, et al. 2014), which used a more conservative approach to exposure estimation.

3.1.3 Synthesis of Epidemiology Studies: Evaluation of the Most Specific Diagnosis

The NRC (2011) raised the issue that diverse types of leukemias and lymphomas should not be grouped "because it combines many diverse cancers that are not closely related in etiology and cells of origin. Although the draft IRIS assessment explores specific diagnoses—such as AML and CML, as well as Hodgkin lymphoma and multiple myeloma (see, for example, EPA 2010, Table 4-92)—the determinations of causality are made for the heterogeneous groupings of "all LHP cancers," "all

leukemias," and "ML". When results for heterogeneous groupings are presented, there is no evidence of increased risk of all LHP cancers (Meyers, et al. 2013; Bean Freeman, et al. 2009) or all leukemias combined (Coggon et al. 2014; Meyers et al. 2013; Beane Freeman, et al., 2009) in industrial cohorts when compared to general mortality rates. In addition, there is no evidence of exposure-response associations between all LHPs combined (or all leukemias combined) and cumulative exposure or average exposure (Beane Freeman, et al. 2009) or duration of exposure (Meyers, et al., 2013; Coggon, et al., 2014).

Interestingly, the EPA IRIS Draft (2010) noted that "Acute leukemias (ALL and AML), believed to arise from transformation of stem cells in the bone marrow, are less plausible. In contrast chronic lymphatic leukemia, lymphomas, multiple myelomas (from plasma B cells), and unspecified cancers may involve an etiology in peripheral tissues to include cells, cell aggregates, germinal centers, and lymph nodes. An association of these cancers to an exogenous agent acting at the POE [portal of entry] is biologically plausible" (page 4-190).

While the etiologies of most LHM are poorly understood, the possible role of environmental agents is plausible for AML, which has been linked with benzene, tobacco smoking, ionizing radiation and various cancer treatment agents, such as cisplastin, all of which have been classified by IARC as known human carcinogens that cause AML. It should stressed, however, that evidence exists that these agents, or their carcinogenic components, are capable of reaching the bone marrow. However, only six epidemiological studies of workers substantially exposed to formaldehyde published to date have published AML-specific results (Blair, et al. 2001; Checkoway, et al. 2015; Hauptmann, et al. 2009; Meyers, et al. 2013; Saberi Hosnijeh, et al. 2013; Talibov, et al. 2014), four of which were not available at the time of the IARC review or the release of the EPA IRIS Draft. Saberi Hosnijeh et al. (2013) reported no association between "low" formaldehyde exposure and incidence of myeloid leukemia HR 1.02, 95% CI 0.72-1.42 based on 49 cases exposed to formaldehyde and 130 unexposed cases). No differences

were seen between subtypes: AML (HR 1.01, 95% CI 0.65 - 1.57) or CML (HR 0.92, 95% CI 0.46-1.84). No myeloid case (and therefore no AML cases or CML cases) occurred among those classified as having "high" formaldehyde exposure (Saberi Hosnijeh, et al. 2013). Talibov et al. (2014) found no association between formaldehyde and incident AML, after adjusting for exposure to specific solvents and ionizing radiation (HR 1.17, 95% CI 0.91-1.51 for 136 workers and 628 controls exposed to > 1.6 ppm-yrs). Meyers et al. (2013) reported a SMR for AML of 1.22 (95% CI 0.67-2.05) based on 14 observed AML deaths. Checkoway et al. (2015) performed AML-specific analysis using the NCI cohort, which had provided results only for all ML combined (Beane Freeman, et al. 2009). When compared to US referent rates, AML mortality risk was found to be decreased among workers exposed to formaldehyde (SMR 0.80, 95 %CI 0.46 - 1.14) and internal analysis of exposure reported no trend with increasing cumulative exposure or peak exposure categories (Checkoway, et al. 2015). Thus, new analyses of the NCI formaldehyde workers cohort specifically for AML detract from the hypothesis that formaldehyde causes AML.

The associations reported by Beane Freeman et al. (2009) between formaldehyde exposure and Hodgkin lymphoma and CML have not been observed in other studies (Meyers, et al. 2013; Saberi Hosnijeh, et al. 2013); and are less plausible, given the lack of known associations with CML and other chemicals or agents, such as benzene (Checkoway, et al. 2015). Saberi Hosnijeh et al. (2013) reported a RR of 0.92 (95% 0.46 to 1.84) based on 46 CML cases. Meyers et al. (2013) reported a SMR of 1.35 (95% CI 0.44-3.15), based on 5 CML cases through 2008. The absence of established toxicological mechanisms for formaldehyde exposure and any of the LHM further weakens arguments for causation (Checkoway, et al. 2012, 2015), especially given that inhaled formaldehyde appears incapable of reaching the bone marrow (discussed below).

3.2 **Toxicological Evidence**

3.2.1 Animal Evidence of Formaldehyde-Induced LHM

With regard to animal evidence of formaldehyde-induced LHM, the EPA (2010) IRIS document indicated that the available animal evidence is limited, discussing mainly the results from the Battelle Columbus Laboratories (1981) study. The EPA (2010) IRIS document indicates that this study provides the only evidence of formaldehyde-induced LHM in animal models. However, the NRC (2011) Committee indicated that although intriguing, EPA's unpublished re-analysis of the Battelle chronic experiments in mice and rats (Battelle Columbus Laboratories 1981) contributes little to the weight of evidence evaluation.

In rats, Battelle Columbus Laboratories (1981) reported the incidence of leukemia (most of which were diagnosed as undifferentiated leukemia found sporadically in various organs) in male and female Fischer 344 rats following exposure to concentrations of 0, 2, 6, or 15 ppm for 24 months, followed by 6 months with no exposure. No concentration-related increases in the incidences of leukemia in either sex of rats were reported by Battelle Columbus Laboratories (1981), when a standard Fisher-Irwin exact test was applied (males p=0.0972; females p=0.2316).

Because of a significant number of early deaths in the high concentration group of both males and females, Battelle Columbus Laboratories (1981) also applied Tarone's extension to the Cox log-rank test (Tarone 1975) to evaluate the leukemia incidence data. This test accounts for the number of animals at risk at each time point when the response of interest is observed. This adjustment assessed the probability of developing the endpoint of interest in those animals that did not survive until the termination of the study. The results of Tarone's extension indicated that the incidence among female

rats in the high concentration group were statistically significant (p=0.0056, not 0.0003 as reported[3]); however, no association was seen in the male rats exposed at high concentrations (p=0.6891). No concentration-related increase in leukemia was observed in the female rates exposed at 2 ppm or 6 ppm, and no survival problems were noted. Even after application of Tarone's extension, all leukemia in male or female rats was not identified in the Battelle Columbus Laboratories (1981) study as an endpoint related to formaldehyde exposure, nor was it so designated in two publications citing this study (Kerns, et al. 1983; Swenberg, et al. 2012).

More contemporary, statistical methods, such as the Cochran-Armitage and the Poly3 (Bailer and Portier 1988; Peddada and Kissling 2006) trend tests, have replaced those used in the early 1980's. The Poly3 trend test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take inter-group survival differences into account. Importantly, the Poly3 test is the test currently used by the National Toxicology Program (NTP) to evaluate incidence data both for trend and pair-wise comparisons, to assess the probability of the response in the presence of inter-current mortality. The results of the application of these tests indicated p values of 0.43 and 0.82 for the Poly3 and Cochran-Armitage, respectively, demonstrating no association.

In mice, the EPA (2010) Draft IRIS Assessment suggests that the "adjusted" incidence of lymphoma in female mice, when the 6-month sacrifice animals were removed from consideration (because tissues outside of the respiratory tract were not examined), was statistically significant ($p<0.05$) in animals exposed to 15 ppm formaldehyde, compared to untreated controls. However, as indicated in the methods for the Battelle Columbus Laboratories (1981) study, statistical significance, when applying the Tarone extension of the Cox test, is achieved with a p value of p=0.05 divided by the number of dose

[3] This appears to be a misreading of the Battelle report. In the Battelle Report Volume A Table 10 – Analysis of Effects of Formaldehyde in Female Rats - reports a p-value of 0.0056 from the Adjusted Cox/Tarone pair-wise comparison of the control to 15 ppm for Leukemia, all. The next row in that table with an endpoint of Uterus, Endometrial Stromal Polyp is the one that reports a p-value of 0.0003 for the pair-wise analysis of control to 15 ppm.

groups. In the case of the Battelle Columbus Laboratories (1981) study for the mouse data, statistical significance would be $p<0.0167$, as noted in the summary tables (Table 8 of the Battelle Columbus Laboratories (1981) report); therefore, based on this criterion, this endpoint was not considered statistically significant. As with the leukemia incidence in rats, the Battelle study authors did not report lymphoma in mice as an endpoint related to formaldehyde exposure.

Since 2010, two short-term carcinogenicity studies have been conducted and published (as a Technical Report) by the NTP of NIEHS in strains of genetically predisposed mice (male C3B6.129F1-Trp53tm1Brdp53 haplo-insufficient mice and male B6.129-Trp53tm1Brd) (Morgan, et al. 2017). These short-term carcinogenicity studies were conducted to test the hypothesis that formaldehyde inhalation would result in an increased incidence and/or shortened latency to nasal and lymphohematopoietic tumors in and to investigate hypotheses that formaldehyde may induce leukemia by a mechanism not involving DNA adduct formation. This proposed mechanism assumes that inhaled FA could cause significant genetic damage to stem cells in the nasal epithelium or circulating in local blood vessels. These damaged stem cells could reach the general circulation, home to tissues that support the hematopoietic niche, undergo lodgement and become leukemic stem cells. The animals were exposed to 7.5 or 15 ppm formaldehyde 6hr/day, 5 days/wk, for 8 weeks. The investigators reported that because the doubling time for hematopoietic stem and progenitor cells (HSPCs) is between 2 and 4 weeks, and the entire HSPC pool turns over every 8 weeks, an 8 week exposure duration was considered sufficient to investigate the hypothesized mechanism for inducing leukemia. Following the 8-wk inhalation exposure, mice were monitored for approximately 32 weeks (until approximately 50 weeks of age). At the highest concentrations, significant cell proliferation and squamous metaplasia of the nasal epithelium were observed; however, no nasal tumors were observed. No cases of leukemia were seen in either strain and a low incidence of lymphoma in exposed mice was not considered related to exposure. In addition, no significant changes in hematological parameters were noted. Under the

conditions of these studies, the authors concluded that formaldehyde inhalation did not cause leukemia in these strains of genetically predisposed mice (Morgan et al. 2017).

Overall, the weight of evidence from animal studies in 2010 did not support an association between formaldehyde exposure and LHM. Since that time, additional studies (Morgan, et al. 2017) have provided evidence that suggests a lack of association between formaldehyde exposure and LHM. In addition, no evidence of changes in blood parameters that might be associated with leukemias has been reported in any animal studies exposed to formaldehyde at high concentrations following both acute and chronic durations (Appelman, et al. 1988; Dean, et al. 1984; Johannsen, et al. 1986; Kamata, et al. 1997; Kerns, et al. 1983; Til, et al. 1988, 1989; Tobe, et al. 1989; Vargova, et al. 1993; Woutersen, et al. 1987). Among these studies, Vargová et al. (1993) reported *increased* red blood cell counts and *increased* proportions of lymphocytes and monocytes in rats, rather than decreases, and this follows exposure to formaldehyde by gavage at 80 mg/kg/day for 28 days.

3.3 ***Mode of Action Evidence***

3.3.1 Improve understanding of when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations

NRC (2011) recommended that one key improvement to the science would be an understanding of when exogenous formaldehyde exposure altered normal endogenous formaldehyde concentrations. Because formaldehyde is an endogenously present compound, it is important to differentiate the presence of levels that are due to normal metabolic processes, from levels that might be present as a result of exogenous exposure. A number of studies have applied sensitive methods to differentiate exogenous and endogenous levels of formaldehyde in tissues (Casanova-Schmitz, et al. 1984; Lu, et al. 2010, 2011; Moeller, et al. 2011; Swenberg, et al. 2011).

The results of these studies with highly sensitive instruments and accurate assays indicate that inhaled formaldehyde was present in the nasal respiratory epithelium, but not other tissues beyond the site of initial contact. In contrast, endogenous adducts were readily detected in all tissues examined. Moreover, the amounts of exogenous formaldehyde-induced adducts were 3- to 8-fold and 5- to 11-fold lower than the average amounts of endogenous formaldehyde-induced adducts in rat and monkey nasal respiratory epithelium, respectively (Yu, et al. 2015).

An additional study conducted in rats with exposed to ^{13}C-formaldehyde (Kleinnijenhuis, et al. 2013) provided results consistent with those from studies focused on measuring endogenous versus exogenous DNA adducts. In this study, Sprague-Dawley rats were exposed nose-only to 10 ppm ^{13}C-formaldehyde for 6 hours and blood concentrations evaluated during exposure and for 30 minutes following exposure. This study was conducted specifically to investigate the mechanism proposed by Zhang et al. (2010) formaldehyde is absorbed during respiration and could reach any target tissue, such as the bone marrow, via the blood in the form of methanediol to exert its genotoxic activity. Exogenous ^{13}C-formaldehyde was not detectable in the blood of rats either during or up to 30 min after the exposure. The authors concluded that "it is highly unlikely that the mechanism proposed by Zhang et al. (2009), that exposure to FA by inhalation may lead to an increased FA concentration in blood and as such may cause leukemia, is true" (Kleinnijenhuis, et al. 2013).

New studies have been conducted to investigate the potential toxicity/carcinogenicity of endogenous formaldehyde. The most recent studies demonstrate that endogenous formaldehyde in bone marrow is toxic, and probably carcinogenic, and may increase leukemia risk (Gao, et al. 2017; Lai, et al. 2016).

3.3.2 Reconcile divergent statements regarding systemic delivery

Multiple studies in multiple species - rats (Lu, et al. 2011; Yu, et al. 2015), monkeys (Moeller, et al. 2011; Yu, et al. 2015), *in vitro* studies of human plasma (Edrissi, et al. 2013) - conducted with a sensitive

analytical method that can measure endogenous versus exogenous formaldehyde DNA adducts have demonstrated that inhaled exogenous formaldehyde is not systemically absorbed or reaches sites distant from the point of initial contact. In addition to these studies, the available data on the toxicokinetics of formaldehyde suggest that no significant amount of "free" formaldehyde would be transported beyond the portal of entry.

In addition to studies supporting the lack of systemic delivery of formaldehyde, anatomically accurate computational fluid dynamics (CFD) models of the rat, monkey, and human have been applied to evaluate the effects of endogenously present formaldehyde on uptake from the respiratory tract. The consideration of endogenous formaldehyde concentrations in nasal tissues did not affect flux or nasal uptake predictions at exposure concentrations > 500 ppb; however, reduced nasal uptake was predicted at lower exposure concentrations (Schroeter, et al. 2014).

3.3.3 Data are insufficient to conclude formaldehyde is causing cytogenetic effects at distant sites

The modes of action that have been proposed in the Draft IRIS Assessment to cause leukemogenesis rely strongly on the hypothesis that exposure to inhaled formaldehyde can result in cytogenetic effects at sites distant from the portal of entry. While the NRC (2011) noted that numerous studies have shown genotoxic effects in cells exposed *in vitro*, and a few studies have shown positive cytogenetic effects in circulating blood lymphocytes in heavily-exposed workers, they also noted that it is unlikely that these effects are relevant to a possible leukemogenic effect of formaldehyde, particularly at low exposure levels. The potential leukemogenic effect and exposure-response relationships at lower exposure levels have been comprehensively evaluated by Nielsen, et al. (2013, 2017).

One of the key studies cited in multiple agency evaluations as providing evidence of cytogenetic events in the development of leukemias is a study by Zhang et al. (2010). Zhang et al. (2010) compared the prevalence of markers of hematopoietic function and chromosomal aneuploidy among workers

occupationally exposed to formaldehyde with those of a group of unexposed workers in China. Ninety-four workers were included, with 43 workers occupationally exposed to formaldehyde and 51 workers unexposed to formaldehyde as controls. The authors reported a higher prevalence of monosomy 7 (loss of a chromosome) and trisomy 8 (gain of a chromosome) in metaphase spreads prepared from cultures of CFU-GM colony cells. The authors suggested that this demonstrated that formaldehyde exposure was associated with an increase in leukemia-specific chromosomal aneuploidy *in vivo* in the hematopoietic progenitor cells of the exposed workers. However, no direct in vivo metaphases had been examined in workers blood. Furthermore, this was a cross-sectional comparison of blood and genetic measures between two groups, and observed differences could not be established as resulting from formaldehyde exposure or due to other overall differences between the two groups.

Two re-analyses of the underlying data from the Zhang et al. (2010) study have been published (Gentry, et al. 2013; Mundt, et al. 2017). The first (Gentry, et al. 2013) relied upon selected underlying data provided through a Freedom of Information Act request that included: 1) individual data on blood cell counts in both formaldehyde-exposed and unexposed individuals including any data on health status of these individuals; 2) individual data on the FISH results for monosomy 7 and trisomy 8 for cultures of samples obtained from 10 formaldehyde-exposed workers and 12 unexposed controls; 3) data on additional chromosomal abnormalities examined and/or observed; and 4) details of the methods sufficient for a qualified scientist to replicate the results reported in the Zhang et al. (2010) study. The results of this reanalysis suggested that factors other than formaldehyde exposure likely contributed to the effects reported. In addition, although the authors stated in their paper that "all scorable metaphase spreads on each slide were analyzed, and a minimum of 150 cells per subject was scored," this protocol was not followed specifically for chromosome 7 or chromosome 8 (recent correspondence indicates a minimum of 150 total metaphases were scored for 24 chromosomes per subject). Far too few cells were counted to draw any meaningful conclusions, and far fewer than the approximately 400

per chromosome cited in previous analyses in which the protocol was described (Zhang et al. 2005; Zhang et al. 2011). In addition, the assays used (CFU-GM) do not actually measure the proposed events in primitive cells involved in the development of AML. Evaluation of these data indicates that the aneuploidy measured could not have arisen *in vivo*, but rather arose during *in vitro* culture.

In 2014, Mundt et al. requested the individual exposure measurement data for each of the participants in the Zhang et al. (2010) study from NCI. In 2016, the request was in part granted and the mean formaldehyde estimate for each exposed worker (but not the individual exposure measurement values) was provided via a Technology Transfer Agreement (TTA) with NCI. Using these data, the Gentry et al. (2013) reanalysis was extended to include exposure-response analyses. Results of this second reanalysis showed that differences seen at the group comparison level, i.e., comparing the prevalence of white blood cell, granulocyte, platelet, and red blood cell counts at the group level in fact were independent of measured formaldehyde exposure level. Among exposed workers, no association was observed between individual average formaldehyde exposure estimates and frequency of aneuploidy, suggested by the original study authors to be indicators of ML risk. Differences between the two groups of workers, other than formaldehyde exposure, were therefore likely to explain the results reported by Zhang et al. (2010).

Subsequent studies of the same population of formaldehyde-exposed and non-exposed workers in China (Lan, et al. 2015; Seow, et al. 2015; Bassig, et al. 2016) have been suggested by the authors to confirm the results of Zhang, et al. 2010; however, many of these studies report results from the same biological samples as Zhang et al. (2010) and therefore, do not provide replication of the results. The repeated use of the original Zhang et al. (2010) data, and its implications, have been reiterated (Mundt, et al. 2017b (in press); Pira, et al. 2017; Gentry, et al. 2013; Speit, et al. 2010) and the original authors have responded to some of the criticisms (Rothman, et al. 2017; Lan, et al. 2015; Zhang, et al. 2010b). Replication of the results of the Zhang et al. (2010) results will require replication in an independent

population of formaldehyde-exposed workers, and where methodological issues are adequately addressed. An attempt to replicate the results could be conducted in the same population of workers as Zhang, et al. (2010) and Lan, et al. (2015) in which the median exposures to 43 workers were 1.28 ppm (10th and 90th percentile: 0.63, 2.51 ppm). However, as noted previously (Section 3.1.1), no evidence of an association between formaldehyde exposure and leukemias have been reported in multiple recent epidemiological studies with large numbers of subjects that have been exposed to concentrations >2.0 ppm. The increasing evidence that inhaled formaldehyde does not move beyond the portal of entry (Section 3.3.2) also calls into question many of the conclusions from the Zhang et al. (2010).

Albertini and Kaden (2016) reviewed the body of data that reportedly indicates genetic changes in circulating blood cells and in blood-borne hematopoietic precursor cells (HPCs). These changes have been considered to be indicators that systemic genotoxicity does occur after human inhalation exposure to formaldehyde, although the mechanisms by which this could occur remain unknown. For each study, the authors examined the sources of exposure, possible co-exposures, biomarkers for internal exposures and genetic signatures of formaldehyde effects.

In reviewing the available studies, many genetic changes in blood cells were noted by Albertini and Kaden (2016), with a contrast in results between animal and human studies: the majority of animal studies were negative and the majority of human studies were positive. This pattern was attributed to the difference in target cell being studied, with bone marrow cells studied in animals and peripheral blood lymphocytes studied in humans. Exposure of human cells to formaldehyde at sites of contact *in vivo* could provide opportunities for exposure of T-lymphocytes to formaldehyde or products of oxidative stress, which could result in the genetic changes observed in peripheral blood cells. However, these results are inconsistent with results from controlled animal studies, discussed previously, that demonstrate - by labeling and administered formaldehyde - inhaled (exogenous) formaldehyde does not travel beyond the portal of entry (Casanova-Schmitz, et al. 1984; Lu, et al. 2010, 2011; Moeller, et al.

2011; Swenberg, et al. 2011). Therefore, these types of genetic changes reported in human studies do not provide evidence that formaldehyde moves beyond the portal of entry to the bone marrow, which would be necessary to result in direct induction of chromosome-level mutations in the bone marrow. Despite the apparent inability of exogenous formaldehyde to reach the bone marrow, the mutagenic effects of formaldehyde in bone marrow have not been tested in humans.

Albertini and Kaden (2016) concluded that overall, the available literature on genetic changes following formaldehyde exposure did not provide convincing evidence that exogenous exposure, and specifically exposure by inhalation, induce mutations as a direct DNA-reactive effect at sites distant from the portal-of-entry tissue. This would include proposed mode of actions that involve effecting a stem cell at the portal of entry with circulation back to the bone marrow. Such exposures have not been shown to induce mutations in the bone marrow or in any other tissues beyond the point of contact. Thus, the weight of scientific evidence does not provide biological plausibility of lymphohematopoietic cancers, as proposed by EPA (2010) and NTP (2011).

3.4 ***Dose-Response Assessment***

Several NRC (2011) peer-review comments were raised regarding the dose-response assessment conducted by EPA in the IRIS Draft Assessment (2010). One comment highlighted the need to conduct independent analyses of the dose-response models conducted, using the data from the Beane Freeman et al. (2009) study to confirm the degree to which the models fit the data appropriately (NRC 2011). Using the original data from the key study (Beane Freeman, et al. 2009) and documentation provided in the draft IRIS profile, Van Landingham, et al. (2016) attempted to duplicate the reported inhalation unit risk (IUR) values for Hodgkin lymphoma and all leukemias and address the NRC Committee's questions regarding application of the appropriate dose-response model. Overall, there was difficulty duplicating

the IURs reported by EPA (2010), largely due to a lack of critical information provided in the IRIS documentation. Perhaps most problematic, the first step of the analysis did not determine significant exposure-response relationships between formaldehyde and lymphohematopoietic endpoints for the metric (cumulative exposure) needed in the estimation of an IUR. The authors concluded that the resulting analysis, while it could be mechanically performed, provided no valid or useful insights on the risks of formaldehyde exposure. The lack of apparent exposure-response relationships for selected endpoints, raises the question whether quantitative analyses are appropriate for these endpoints, and if so, how results are to be interpreted.

The NRC (2011) also noted the need to consider alternative extrapolation models for analyzing the cancer data. In 2013, Starr and Swenberg (2016) proposed a novel "bottom-up" approach for bounding low-dose human cancer risks using formaldehyde as an example. This approach requires information on background risk, background or endogenous exposure and the additional exogenous exposure of interest. The results of this approach provided estimates of risk ($<3.9 \times 10^{-6}$) that were more than 14,000-fold lower than the corresponding EPA (2010) estimate for all leukemias (5.7×10^{-2}) and considers the impact of background endogenous formaldehyde concentrations, which is not considered in the draft EPA (2010) IRIS assessment. In 2016, Starr and Swenberg provided an update to this approach, incorporating new formaldehyde-DNA adduct data, and allowing for uncertainty in two of the parameters (background cancer risk and background endogenous concentrations of formaldehyde). Consideration of the statistical uncertainty in these two parameters resulted in estimates of risk for leukemias that were even smaller than those initially estimated in Starr and Swenberg (2013). The authors concluded that these estimates provide a reality check for the draft EPA IRIS (2010) values. In addition, the large discrepancy between results using an approach that relies on molecular dosimetry data (i.e., the bottom up approach) versus one that relies upon uncertain retrospective occupational

exposure reconstructions (i.e., the approach relied upon in EPA (2010), call into question the credibility of attributing increases in human mortality from leukemias to occupational exposure to formaldehyde.

3.5 ***Methods for Evidence Integration***

The NRC (2011) noted that the Draft IRIS Assessment's (2010) approach to weight of evidence should include "a single integrative step after assessing all of the individual lines of evidence". Although a synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and how that evidence was integrated into a final conclusion are not apparent in the draft assessment and should be made clear in the final version.

Since the EPA Draft (2010) and the NRC (2011) peer review, several frameworks have been developed to integrate evidence across different lines of scientific inquiry including epidemiology, toxicology and mode of action studies (Adami. et al. 2011; Lavelle, et al. 2012; Linkov, et al. 2015; Rhomberg 2015b; Rooney, et al. 2014; Woodruff and Sutton, 2014). The EPA has also proposed preliminary approaches for integrating evidence in response to the NRC (2011) review of formaldehyde (EPA 2013).

Rhomberg et al. (2011) applied a hypothesis-based weight of evidence approach to evaluate formaldehyde and leukemogenesis, considering how human, animal and mode of action results inform one another. In comparing the potential alternative proposals for causality, the authors concluded that the evidence for a causal association between formaldehyde exposure and leukemia is not only weak but strains biological plausibility (Rhomberg, et al. 2011).

Nielsen, et al. (2017) also considered the body of formaldehyde research while re-evaluating the WHO (2010) formaldehyde indoor air quality guideline for cancer risk assessment. Nielsen, et al. (2017) iterated that although formaldehyde is genotoxic and causes DNA adduct formation, it is also

clastogenic. Exposure-response relationships from both animal and human data were nonlinear, and relevant genetic polymorphisms had not been identified. Epidemiological studies had inconsistently reported associations with nasopharyngeal cancer and leukemia; however, relative risks were not increased below 1 ppm (mean exposures). Because inhaled formaldehyde does not pass beyond the respiratory epithelium, any direct effects are limited to portal-of-entry effects (Nielsen, et al. 2017).

Other reviews and syntheses of evidence focused on epidemiological studies, and this body of literature has been most variably interpreted. In 2014, an independent National Research Council committee was charged with peer-reviewing the NTP evaluation of formaldehyde for the 12th revision of the RoC (NRC 2014b). This NRC committee produced a new definition for "sufficient evidence" of carcinogenicity as demonstrated by two or more strong or moderately strong studies with different study designs and populations showing associations between formaldehyde exposure and a specific cancer type. In this approach, "strong" epidemiology studies do not refer to the magnitude of the association, but is a judgment of study quality and utility made by reviewers who considered chance, bias, and confounding as alternative explanations for the observed association and found these were not reasonable explanations. Further, "strong" epidemiology studies comprised large populations with long durations of exposure and an adequate follow up period to allow for latency, and had exposure assessments that were able to discriminate between "high" and "low" formaldehyde exposure categories. This "strength of evidence" approach contrasts with a "weight of evidence approach." Although each epidemiology study was judged as one of three categories (strong, moderately strong, or weak), this approach suggests that 2 or more strong or moderately strong studies with positive results are enough to conclude sufficient evidence of carcinogenicity exists, and discounts epidemiology studies that are negative or contradicting, as well as animal studies that are negative or contradicting.

Meta-analyses are often used to synthesize findings across many epidemiology studies, identifying sources of potential heterogeneity which then can be explored in interpreting the overall evidence. The

EPA considered meta-analyses conducted by Zhang, et al. 2009; Collins and Lineker, 2004, and Bosetti, et al. 2008. Since then, two additional meta-analyses were conducted (Bachand, et al. 2010; Schwilk, et al. 2010). Bachand, et al. (2010) excluded lower-quality studies and reported a meta-RR of 1.05 (95% CI 0.93 - 1.20) based on 16 cohort studies and a meta-OR of 0.99 (95% CI 0.71 - 1.37) based on 2 case-control studies for all leukemia, reported separately due to heterogeneity. Schwilk, et al (2010) published a meta-analysis of the epidemiological findings on myeloid leukemia, but limited to the highest-exposed sub-group reported in four studies (three cohort and one case-control): RR=2.47; 95% CI, 1.42 to 4.27. Checkoway, et al. (2012) conducted a critical review and synthesis of the epidemiological evidence and concluded that results from epidemiological studies were not consistent and did not show strong results or exposure-response associations. None of these reviews, however, included the results from the extended follow up of the NIOSH garment workers study (Meyers, et al. 2013) the extended follow up of the UK producers and users (Coggon, et al. 2014) or the extended analyses of the NCI cohort (Checkoway, et al. 2015). In addition, meta-analyses and/or critical reviews of epidemiological literature require further integration with other lines of evidence.

4.0 Conclusions

It has been seven years since the release of the EPA (2010) Draft IRIS Toxicological Assessment for Formaldehyde. In peer-reviewing this draft report, an NRC (2011) Committee raised many substantive questions related specifically to the conclusions drawn in the document and the quantitative estimates of potential toxicity. This Committee was limited to the information provided in the assessment, and did not independently conduct a review of the primary literature, but did determine that many of EPA's conclusions were not supported by the information and studies cited in the draft assessment. The committee also identified general methodologic problems with the IRIS Draft Assessment, and provided specific comments related to the evaluation of specific studies and conclusions based on the available

evidence. The comments related to a causal association between formaldehyde exposure and LHM largely involved the interpretation of the available evidence at that time and the framework in which it was evaluated by EPA (2010). The committee found that EPA's preliminary conclusion that formaldehyde causes leukemia, ML or related hematopoietic cancers appeared to be "subjective' in nature, and that no clear scientific framework had been applied by EPA in reaching that conclusion. The absence of such a framework was judged by the committee as troublesome, given that the scientific evidence on the question was very weak (NRC 2011).

Since the 2011 NRC Peer Review, significant additional scientific evidence has become available that addresses many of the questions raised by the NRC Committee regarding a causal association between formaldehyde exposure and LHM. Some of these new studies and analyses were conducted in response to their comments, while others reflect ongoing work and updates of studies on this topic. All add to the scientific evidence surrounding the potential causal relationship between formaldehyde inhalation exposure and LHM, and should be addressed in the critical evaluations and integration of evidence presented in an updated IRIS Assessment.

Also since the NRC Peer Review (2011) of the Draft IRIS Assessment, the EPA has proposed a new IRIS process that incorporates many of the general recommendations made by the NRC (2011, 2014a) related to methodological issues. This process involves the evaluation and synthesis of evidence within separate streams of evidence (human, animal and mechanistic). However, in a critical review of the process conducted by a separate NRC (2014a) Committee, while there was improvement in guidelines for evaluation and synthesis of evidence within an evidence stream, the NRC (2014a) Committee still noted limitations in synthesizing or integrating evidence across streams or categories.

Nearly all of the recently available evidence from multiple lines of evidence, especially those studies that have been focused on addressing comments from the NRC (2011) Committee reviewing the Draft IRIS

Assessment, have increased the weight of evidence favouring a conclusion of a lack of a causal association between formaldehyde exposure and LHM. The Checkoway et al. (2015) re-analysis using the raw data from the Beane Freeman et al. (2009) study was able to address directly several questions and comments from the NRC (2011) Committee, as the Draft IRIS Assessment (2010) was highly dependent on its interpretation of this study for drawing both qualitative and quantitative conclusions related to formaldehyde leukemogenicity and risk of LHM following inhalation exposure to formaldehyde. The Checkoway et al. (2015) reanalysis provides several results and insights relevant for assessing the risk of individual LHM. Not the least of these, the AML specific results provide no support for the conclusion that formaldehyde causes AML. Associations seen between formaldehyde exposure and Hodgkin lymphoma and CML are inconsistent with other studies and also lack a plausible biological mechanism (Checkoway et al. 2015). NTP (2011) also noted that because the evidence for Hodgkin lymphoma is mainly limited to the NCI cohort study, a causal association cannot be established. No other LHM was associated with either cumulative or peak formaldehyde exposure. These results of the fuller analysis of the data from Beane Freeman et al. (2009) are consistent with recent epidemiological studies (Meyers, et al. 2013; Saberi Hosnijeh, et al. 2013; Talibov, et al. 2014) which report no significant increase in LHM, specifically AML, among cohorts of workers exposed to formaldehyde.

The available animal evidence did not support a causal association between formaldehyde exposure and LHM at the time the EPA Draft (2010) was released. Since that time, two additional studies have been conducted by the NTP (Morgan 2017) using two sensitive assays in mice genetically predisposed to develop cancer following short-term exposure to a chemical. These studies provided no evidence of changes in endpoints related to LHM or the presence of any LHM following exposure to high concentrations (15 ppm) of formaldehyde.

Studies conducted to evaluate potential mechanisms associated with formaldehyde exposure and LHM have demonstrated a lack of evidence for exogenous formaldehyde to move beyond the portal of entry.

Multiple studies conducted in multiple species using a highly sensitive technique (Edrissi, et al. 2013; Lu, et al. 2011; Moeller, et al. 2011;Yu, et al. 2015) have demonstrated that while endogenous formaldehyde is present in all tissues, exogenous formaldehyde following inhalation exposure is not transported systemically. While some mechanisms for the development of LHM following inhalation exposure to formaldehyde have been hypothesized (EPA 2010; Zhang, et al. 2009, 2010), there is no evidence to support these proposed mechanisms and the NRC (2011) Committee noted that:

> "Although EPA postulated that formaldehyde could reach the bone marrow either as methanediol or as a byproduct of nonenzymatic reactions with glutathione, numerous studies described above have demonstrated that systemic delivery of formaldehyde is highly unlikely at concentrations below those which overwhelm metabolism according to sensitive and selective analytic methods that can differentiate endogenous from exogenous exposures."

The more recent research all but confirms this. Several modes of action have been proposed, relying primarily on data reported by Zhang et al. (2010) as well as subsequent evaluations of the same population of Chinese workers (Bassig, et al. 2016; Lan, et al. 2015; Seow et al. 2015). These include a mode of action in which risk of ML is increased due to immune suppression resulting from formaldehyde exposure (Bassig et al. 2016; Seow et al. 2015). The speculated modes of action, however, assume systemic delivery of formaldehyde except one, which is a hypothesized mode of action in which hematopoietic cells in the nasal epithelium that are impacted by exposure to formaldehyde return to the bone marrow. The NRC (2011) Committee considered this proposed mode of action and concluded that:

> "As a result, EPA could only speculate that circulating hematopoietic stem cells that percolate through nasal capillary beds or nasal-associated lymphoid tissues may be the target cells for

mutations and clastogenic effects that eventually result in lymphohemotopoietic cancers. Experimental evidence of [this] mechanism is lacking."

This currently leaves no acceptable proposed mode of action for the development of LHM following inhalation exposure to formaldehyde that can be scientifically substantiated.

The available toxicokinetic data also do not support the transport of inhaled formaldehyde from the portal of entry. The studies by Swenberg and colleagues unequivocally demonstrate that exogenous formaldehyde exposure does not increase formaldehyde concentrations measured in any internal tissues over those in unexposed animals, i.e., endogenously produced formaldehyde is the predominant if not only source of internal formaldehyde (Edrissi, et al. 2013; Lu, et al. 2010, 2011; Moeller, et al. 2011; Swenberg, et al. 2011; Yu 2015).

The biological plausibility of a mode of action for the development of LHM following inhalation exposure to formaldehyde has relied heavily upon the incomplete results from the Zhang et al. (2010) study in which the authors report differences between groups of formaldehyde exposed and unexposed groups in the frequency of monosomy 7 (loss of chromosome) and trisomy 8 (gain of chromosome), based on metaphase spreads prepared from culture of CFU-GM colony cells. However, reanalysis of the underlying raw data in two studies (Gentry, et al. 2013; Mundt, et al. 2017) have identified methodological problems with this study that challenge these conclusions, as well as demonstrate a lack of association between level of formaldehyde exposure and the observed aneuploidy (or any of the haematological measures).

Overall, the quality and amount of evidence relevant to the understanding of a potential causal relationship between formaldehyde inhalation exposure and risk of LHM has increased substantially since the completion of the EPA (2010) Draft IRIS Assessment and release of the 2011 NRC Peer Review of the Draft Assessment. New evidence has been published in each of the major streams of evidence

(i.e., human, animal and mechanistic) that consistently indicates a lack of a causal association between formaldehyde exposure and LHM, and specifically AML. These new studies have addressed many of the NRC (2011) criticisms surrounding the evaluation of a combination of cancer types, as well as increased our understanding of the potential impact of exogenous exposure on endogenous levels, which is critical in attempting to understand the potential hazards or risks from formaldehyde exposure. Regardless of which of the several similar approaches to integrating the available evidence between formaldehyde inhalation exposure and the potential for leukemia risk, there is at most only limited suggestive positive evidence, in contrast with the bulk of evidence suggesting no such association. Therefore, a conclusion of causation is not justified scientifically. The scientific landscape into which EPA will release its long-anticipated revised IRIS Toxicological Review of Formaldehyde – Inhalation Assessment is very different from that of the 2010 Draft IRIS Assessment, both in terms of improved methodological approaches and the available epidemiological, toxicological and mechanistic evidence. Given formaldehyde's commercial importance, ubiquity in the environment and endogenous production, accurate determination of whether exposure to formaldehyde from occupational, residential and consumer products causes leukemia or any type of human neoplasm is critical.

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